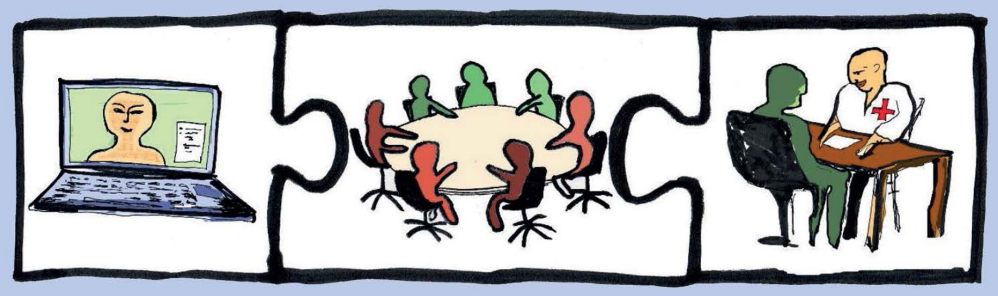
Cardiovascular risk management for patients with a severe mental illness

Kirsti Jakobs



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Kirsti Jakobs

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Chapter 1

Introduction



1. Severe mental illness and its cardiovascular risk

Severe mental illness (SMI) refers to mental disorders that are so debilitating that they significantly impair patients' ability to engage in functional and occupational activities. Patients with an SMI are more likely to have comorbid somatic conditions[1]. There is substantial evidence that individuals with an SMI have a life expectancy that is 10-25 years shorter than the average population[2-6], with premature cardiovascular deaths being the most important cause of this disparity[7-9]. The reasons for poor health outcomes among people with SMI are multifaceted. They include stress resulting from mental illness and related social issues[10], drug and alcohol problems[11], negative effects of medications, especially antipsychotics (APs)[12,13], and unhealthy lifestyle choices[14-17]. Additionally, inequities in access to healthcare among patients with SMI contribute to poor health outcomes[18-20]. All these factors combined lead to patients with an SMI having a 78% higher risk of developing cardiovascular diseases, and an 85% higher risk of dying from cardiovascular diseases, compared to the regionally matched general population[13].

In 2011, the prevalence of SMI, as defined by Delespaul and colleagues (see section 2), was estimated to be 1.7%, corresponding to 281,000 Dutch citizens[21]. In 2012, the national government, healthcare providers, health insurers, and client organizations in the Netherlands, agreed on a care shift for patients with SMI from institutes to ambulant care[22]. Due to this policy, intramural care decreased by 31% between 2009 and 2020[23]. This has not resulted in an equivalent increase in the use of intensive ambulant care teams. There has also been a shift from specialist mental healthcare to primary care, with many patients with a stable SMI being referred back from specialist mental healthcare to their general practitioner (GP). At the same time, mental health nurses were introduced in general practices. These nurses assist patients with minor mental health problems, provide short-term treatment, and refer patients through triage and screening. Between 2015 and 2018 the number of adult patients who contacted mental health nurses in general practice increased by 25.6%, thus helping 537.040 of 1.350.581 patients with minor mental health problems[23]. In the current organization of general practice, the involvement of mental health nurses in the care of patients with SMI is generally reactive[24]. The amount of patients with an SMI who depend exclusively on the general practice for their mental health is not known.

The Dutch multidisciplinary guideline of care for people with SMI, published in 2017, recommends an integrated approach that involves recovery and reintegration into society,

along with psychiatric and psychological treatment[25]. It advises to conduct annual physical health screenings, medication evaluations, and lifestyle assessments. Based on the results of these screenings, mental health practitioners or GPs, along with the patient and their family members, should collaborate to develop a plan for managing the patient's physical health. Additionally, if necessary, lifestyle interventions should be implemented[25]. Mental healthcare providers are familiar with this care guideline; however, it is unclear to what extent GPs are. There are no specific guidelines for the treatment of SMI in general practice. It is unclear whether and to what extent GPs can provide the right care to this group. Ideally, this care would include the prevention and management of cardiovascular diseases, identifying needs for referrals to community support, and a medication review particularly if patients use APs.

In the Netherlands, GPs are increasingly taking on the role of primary healthcare providers for patients with an SMI. However, the extent to which Dutch GPs monitor and treat preventable cardiovascular risk (CVR) in these patients is currently unknown. At the outset of our research, we hypothesized that their efforts in this area would be minimal. Consequently, we aimed to systematically investigate how primary care can help prevent cardiovascular disease in patients with an SMI.

Fictive case

Mrs. D, who has been my patient for a long time, is 49 years old, married, and has two sons. The first diagnosis in her file is 'borderline personality disorder'. Her arms are full of old scars due to auto-mutilation. In the past, she often suffered from depression, but she never had a psychotic episode as far as I know. She has been rather well in the last few years. Her sons, who also suffer from mental health problems (one has autism and an intellectual disability, and the other has an attention deficit hyperactivity disorder), are adults now and live in supervised housing. She has been in 'dialectical behavior therapy' and 'schema-focused therapy' for a long time in a frequency that changed depending on her symptoms and functional impairment. In 2014 she was referred back to primary care and she has not seen a psychiatrist since. In the past, she had been severely obese. However, due to bariatric surgery, her body mass index was reduced from 52 to 29 kg/m^2. The medications she takes at this moment are omeprazole 1dd 40 mg, quetiapine 50mg in the morning and 200 mg at night, fluoxetine 60 mg, and laxatives.

As a general practitioner with expertise in cardiovascular disease, I have learned that patients with severe mental illness (SMI) and those taking APs are more at risk of developing cardiovascular disease than others. I believe Mrs. D might have an SMI, considering the long-term nature of her mental health issues. Additionally, I have been prescribing her quetiapine for the past ten years. Therefore, I asked her to visit me to check her cardiovascular risk. The laboratory results came through today. It turns out that her cholesterol is too high. Should I lower her quetiapine? This might also prevent her from becoming more obese again. Would she become unstable if I changed it? According to the risk assessment tool of the general practitioners' guideline on cardiovascular diseases (SCORE2), her CVR is still low. However, her mental illness nor her use of quetiapine are taken into account in this risk assessment tool. Should I wait a couple of years until her CVR goes up? Would the psychiatrist still think quetiapine is the best option for her or have insights changed over time? The psychiatrist did not mention her cholesterol in his referral letter to me. I am struggling.

2. Definition of SMI

In scientific literature, SMI is commonly defined in two ways: a descriptive definition and a diagnostic definition. The descriptive definition, utilized in the Netherlands, was published by a consensus group led by Delespaul[21]:

A mental illness is severe when:

– there is a psychiatric disorder, which makes care or treatment necessary (not in symptomatic remission);

– and with severe social limitations or social functioning (not into functional remission);

– and where the disability is the cause and consequence of a psychiatric disorder;

– and is not transient (structural or long-term, at least several years);

– and where coordinated care from professional care providers in care networks is indicated to realize the treatment plan.

The second definition is based on a specific mental disorder diagnosis. The choice of which diagnoses are included varies in scientific literature[26]. The most used diagnoses are: Schizophrenia or schizoaffective disorder, bipolar disorder, other psychosis or psychotic disorders, and depression (moderate or severe).

The first definition is useful from a clinical perspective. However, using this definition to analyze primary care data lacks replicability. The second definition is more suitable for use in a research setting to define the inclusion criteria of a study. There are two issues faced in Dutch primary care when it comes to using the second definition. First, many patients have an incorrect diagnosis in their medical file due to inadequate information or the wrong diagnostic code. Second, the diagnosis code for depression is also applied to a significant number of patients with minor depression or depression in remission. Therefore, particularly for the studies described in this thesis, we developed a third and new definition in which we modified the second definition to be more suitable for the primary care setting in the Netherlands. This new definition includes:

1. Schizophrenia;
2. bipolar disorder;
3. other psychosis or psychotic disorders;
4. the chronic use of lithium or APs (if not prescribed for delirium or dementia).

This definition will be referred to as SMI in this thesis unless stated otherwise.

The use of this modified definition has several consequences. We chose not to include depression in our criteria because this diagnosis often encompasses a wide range of patients, including those with mild depression or those whose depression is in remission. By excluding depression, we aim to prevent the misclassification of many patients. However, this decision may inadvertently exclude some individuals who have moderate or severe depression. Additionally, we decided to include patients who are chronic users of lithium or APs in our definition. This approach accounts for individuals who may not have the correct diagnosis recorded in their medical records due to insufficient information or improper use of diagnostic codes. Consequently, we included patients who do not have a severe mental illness (SMI) but are prescribed APs off-label.

This inclusion is necessary because the use of APs requires monitoring for potential cardiovascular risks.

3. Antipsychotic medication

APs are highly effective in reducing symptoms and improving the quality of life for acute psychosis, a severe condition characterized by a loss of contact with reality. Psychotic

symptoms can increase patients' risk of harming themselves or others or being unable to meet their basic needs[27,28]. APs are also used in the treatment of chronic psychotic disorders such as schizophrenia, bipolar mania, and other psychiatric conditions[27]. The risk of relapse is reduced with the use of APs. Although the exact underlying mechanisms are not well understood, long-term treatment is linked to improved survival rates for individuals diagnosed with schizophrenia[28,29].

There are two types of APs: classical and atypical APs. Classical APs, like haloperidol, have been used to treat psychosis since 1952. These APs often cause extrapyramidal adverse effects. Atypical APs, like quetiapine and risperidone, were developed in the nineties and do not cause extrapyramidal symptoms. However, long-term use of atypical APs may affect metabolic pathways to a larger extent than classical APs, resulting in weight gain, glucose intolerance, and dyslipidemia, which are risk factors for diabetes and cardiovascular disease[30].

The use of APs has increased by 48% between 2003 and 2022[31]. An increase is also seen in other countries and has multiple explanations[32,33]. One of the explanations is the increase in off-label prescriptions of atypical APs for several diagnoses, including anxiety, ADHD, insomnia, OCD, PTSD, personality disorders, substance abuse, Tourette's syndrome, and autism[34-36]. It is unclear which amount is prescribed by GPs in the Netherlands. In Denmark, around 65% of off-label AP prescriptions are initiated by GPs[34].

4. Cardiovascular risk management in Dutch primary care

Dutch GPs are well organized in regional primary care cooperatives, which aim to provide high-quality chronic disease management in primary care. They provide programs for patients with diabetes mellitus, cardiovascular diseases, high cardiovascular risk (CVR), Chronic Obstructive Pulmonary Disease (COPD), and asthma[37,38]. In these programs, trained practice nurses assist patients with lifestyle interventions and medication management. Health insurance companies fund these programs, and each cooperative provides GPs with access to protocols, information and communication technology, and educational resources for GPs and their nursing staff. The elevated CVR of patients with an SMI was not mentioned in the Dutch GP cardiovascular risk management guideline[39], until the most recent revision in September 2024[40]. Depending on agreements with health insurance companies, in most regions in the Netherlands, the cardiovascular risk management program may not be accessible to patients

with an SMI unless they have other CVR factors acknowledged in the guideline. The most important reason for this may be that there is a lack of evidence about the effectiveness of interventions to mitigate or treat cardiovascular diseases for this patient group in primary care.

5. Aims of this thesis

The case study of Mrs. D brings to light some of the issues GPs face when caring for a patient with an SMI. The aims of this thesis are:

1. To investigate the nature, extent, and challenges of managing cardiovascular risk in primary healthcare for patients with an SMI from the perspective of GPs.
2. To outline the development of TACTIC, an intervention aimed at reducing preventable cardiovascular risk factors in patients with an SMI, and to prepare for trial testing its effectiveness.

TACTIC

Alongside our studies, an interdisciplinary collaboration project called "PLEK voor EPA" was initiated in the Arnhem region in the east of the Netherlands to improve the integrated care for patients with an SMI[41]. The collaboration involved primary care professionals, specialist mental healthcare providers, persons with lived experience, and representatives from the municipality. Persons with lived experience promote care in partnership with patients by providing information about available options for recovery and assistance with reintegration into society while encouraging patient empowerment. In the context of the "PLEK voor EPA" project, two studies were carried out on the effect of multidisciplinary meetings in which patients actively participated. Neither of the studies has been published in peer-reviewed international scientific journals. In one study, the use of APs was the central topic, and the pros and cons were thoroughly evaluated to provide personalized advice to each patient. In the other study, discussions focused on recovery care wishes and opportunities within the neighborhood to improve personal recovery and quality of life[41]. "PLEK voor EPA" is recognized as a good practice example for providing integrated care, addressing both the physical and psychosocial needs of patients with SMI[42]. However, the effects on physical and psychosocial care have not been scientifically studied yet. This example of

multidisciplinary meetings inspired the TACTIC intervention detailed in chapters five to seven. TACTIC is the acronym for: '**T**ransmural collaborative care model for cardiovascular risk management and medication review for patients using **A**ntipsy**C**ho**TIC**s.

6. Outline of this thesis

Chapter 2 explains the need to address cardiovascular risk management for patients on APs.

Chapter 3 examines the current rate of cardiovascular risk screening in patients with an SMI in general practice.

Chapter 4 explores the barriers and facilitators according to GPs on cardiovascular risk management for this patient group.

Chapter 5 presents a complex intervention designed to review the use of atypical APs and advise on CVR-lowering strategies in a transmural collaboration. The acronym of this intervention is TACTIC and the figure on the cover of this manuscript is a simplified representation of the process. The feasibility of TACTIC in terms of potential effects, reach, and attrition rates was studied in this chapter.

In Chapter 6 the views and experiences of the participating patients, persons with lived experience, and professionals about TACTIC are explored in a qualitative feasibility study.

Chapter 7 describes the study protocol to assess the effects of TACTIC in a stepped wedge cluster randomized controlled trial.

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Chapter 2

CVRM in patients using antipsychotics: It is time to take action

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Background

The study from Lai and colleagues, recently published in BMC Medicine provides interesting new insights on sex-related associations between antipsychotic use and acute ischemic heart disease[1]. The authors demonstrated that antipsychotic use was associated with a 32% increased hazard rate of acute ischemic heart disease (IHD) among women (95% CI: 1.05 – 1.67), but not among men. In their Hong Kong primary care population almost 2% were prescribed antipsychotic drugs.

The use of antipsychotic medications is increasing worldwide. Antipsychotics are indicated for the treatment of severe mental illness (SMI), including psychotic and bipolar disorder. Remarkably, a large proportion of patients on antipsychotics do not have a diagnosis of SMI. This off-label use can add up to 60% of antipsychotic prescriptions, particularly for atypical antipsychotic drugs such as olanzapine[2]. Reasons for off-label prescriptions are anxiety, depression, dementia, sleep, and personality disorders[2]. As a result of such increased use, long-term side-effects of antipsychotic drugs may increase the burden on patients and healthcare services globally. Long-term use may affect metabolic pathways, thereby causing weight gain, glucose intolerance, dyslipidemia, and cardiac toxicity, resulting in an increased risk of diabetes, cardiovascular disease, and mortality[3]. Current guidelines on cardiovascular risk management, such as those from the National Institute for Health and Care Excellence (NICE)[4], are particularly relevant for cardiometabolic risk in patients on antipsychotic drugs, specifically atypical antipsychotics. However, risk management in patients on antipsychotics is often performed poorly[5]. A recent study showed screening rates in less than 10% of Dutch primary care patients using antipsychotics[6]. What do the study results of Lai and colleagues add to current clinical guidelines? And do their results support further improvement of cardiovascular risk management implementation?

Variations in side-effects and the influence of patient factors

Lai and colleagues performed a retrospective study using primary care data of over one million patients. A retrospective design, however, is unsuitable to prove causality. Important known intermediate variables, like cholesterol- and blood glucose level, and an unhealthy lifestyle, were not taken into account. Therefore, confounding by indication cannot be ruled out. The same problem occurs with dosage, duration of the use, and the underlying diagnosis.

Research increasingly suggests that patients on antipsychotic drugs are in high need of cardiometabolic risk screening[3]. However, the risk of an individual patient appears to depend on many personal circumstances and variables, which makes estimation of the cardiometabolic risk difficult. A recent meta-analysis on the efficacy and tolerability of 32 oral antipsychotics showed large variations among antipsychotic drugs in metabolic side-effects and that specific patient factors, such as age, sex, and ethnicity, may increase the risk of metabolic dysregulation[7]. Despite the limitations in the study of Lai and colleagues, their results also suggest variations in side effects and the influence of patient factors. The association found between antipsychotic drugs and ischemic heart disease in women weakened and became non-significant after omitting haloperidol, a typical antipsychotic, from the analyses. Variations in side-effects and patient-related factors should be taken into account by healthcare professionals when providing cardiovascular risk management for individuals using antipsychotics.

Cardiovascular risk management

An increased cardiovascular risk in patients taking antipsychotic medications can be better treated in a primary care setting, with lifestyle counselling as well as pharmacological interventions, not differently from managing cardiovascular risk in other patient groups[4]. Besides, primary care has the opportunity to reach a broad population, including patients with mental disorders in a stable phase using antipsychotics and as a consequence not under regular specialist care. However, family physicians may be insufficiently aware of specific antipsychotic side effects, interactions, and relevant patient factors, which may hinder the required personalization of cardiovascular risk management. For instance, dose reduction or switching to an antipsychotic drug with a better metabolic profile are promising strategies to lower cardiometabolic risk. Moreover, barriers in access and communication between family physicians and patients using antipsychotic drugs may further complicate implementation of cardiovascular risk screening and treatment. Healthcare professionals are inconsistent in their approach, and sometimes have negative perceptions towards patients with SMI, for instance regarding smoking cessation. Simultaneously, patients' access to primary care for the target group at issue is often hindered by limited help-seeking behavior, psychological barriers, and poor understanding of preventing physical illness. The complexities regarding implementation

of cardiovascular risk management in patients using antipsychotics require well-designed complex interventions, in which family physicians closely collaborate with patients, psychiatrists, and other disciplines. In this context, consultation liaisons and collaborative care models are options to consider. In consultation liaisons, family physicians maintain the central role in the delivery of care with mental health specialists providing consultative support. The collaborative care model is a broader, more systematic approach that involves the integration of care managers and consultant psychiatrists, controlled by the family physician. Both models have shown positive results in the primary care for people with mental disorders[8], but not on the lowering of cardiovascular risk in this specific population[9]. While developing interventions, healthcare professionals and researchers should consider that the causal chain between a risk lowering intervention and a desired outcome is complex and easily disrupted. The guideline for the development and evaluation of complex interventions of the Medical Research Council may be supportive[10].

Time to take action

Given the complex nature of causal factors (indications for prescription), the unknown impact of the various intermediate factors (pathophysiological and biochemical parameters; lifestyle factors), and unknown effectiveness of the required complex interventions, we argue that the study by Lai and colleagues is exploratory in nature and should be applied carefully in clinical practice. However, the evidence about the considerable risks of antipsychotics is convincing enough to take action and effectively implement cardiovascular risk management interventions, based on collaborative care models and consultation liaisons. Future studies should focus on the development and evaluation of these complex interventions, and include closely monitoring the intermediate variables, to further untangle the roles of antipsychotic drugs in increasing cardiovascular risk.

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Chapter 3

Cardiovascular risk screening of patients with serious mental illness or use of antipsychotics in family practice

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Abstract

Background

Patients with serious mental illness (SMI) and patients on antipsychotics (AP) have an elevated risk for cardiovascular diseases. In the Netherlands, mental healthcare for these patients is increasingly taken care of by family practitioners (FPs) as a result of a shift from secondary to primary care. Therefore, it is essential to increase our knowledge regarding the characteristics of this patient group and the (somatic) care provided by their FPs. The aim was to examine the rate of cardiovascular risk screening in patients with SMI or the use of AP in family practice.

Methods

We performed a retrospective cohort study of 151.238 patients listed in 24 family practices in the Netherlands.

From electronic medical records we extracted data concerning diagnoses, measurement values of CVR factors, medication, and frequency of visits over a 2 year period. Primary outcome was the rate of patients who were screened for CVR factors. We compared three groups: patients with SMI/AP without diabetes or CVD (SMI/AP-only), patients with SMI/AP and diabetes mellitus (SMI/AP+DM), patients with SMI/AP and a history of cardiovascular disease (SMI/AP+CVD). We explored factors associated with adequate screening using multilevel logistic regression.

Results

We identified 1705 patients with SMI/AP, 834 with an SMI diagnosis, and 1150 using AP. The screening rate for CVR in the SMI/AP-only group (n=1383) was adequate at 8.5%. Screening was higher in the SMI/AP-+DM (n=206, 68.4% adequate, OR 24.6 (95%CI, 17.3-35.1) and SMI/AP+CVD (n=116, 26.7% adequate, OR 4.2 (95%CI, 2.7-6.6). A high frequency of visits, age, the use of AP, and a diagnosis of COPD were associated with a higher screening rate. In addition, we also examined differences between patients with SMI and patients using AP without SMI.

Conclusion

CVR screening in patients with SMI/AP is performed poorly in Dutch family practices. Acceptable screening rates were found only among SMI/AP patients with diabetes mellitus as a comorbidity. The finding of a large group of AP users without an SMI diagnosis may indicate that FPs often prescribe AP off-label, lack information about the diagnosis, or use the wrong code.

Background

Both a diagnosis of serious mental illness (SMI) and the use of antipsychotics (AP) are associated with an elevated cardiovascular risk. SMI incorporates schizophrenia, bipolar disorder, and other psychotic disorders.[1] People with an SMI have an 8-20 years shorter life expectancy compared to the general population,[2,3] which is mainly caused by CVD[4-6]. The etiology of the increased risk for CVD in patients with SMI is multifactorial, including high levels of smoking and other substance misuse, poor dietary intake, inadequate amount of exercise, less access to medical care, obesity, diabetes, and adverse effects of AP[6-16]. The use of AP increases the risk of CVD via metabolic pathways involving weight gain, glucose intolerance, and dyslipidemia and can cause cardiac toxicity[4, 17-19]. Patients get AP prescribed for SMI, but a growing group receives AP prescriptions off-label. Main indications for off-label prescription are mood disorders, anxiety disorders, insomnia, and agitation[20].

Guidelines[21-24] and medicine agencies[25,26] recommend annual screening for cardiovascular risk factors in patients with SMI and all patients using AP. Unfortunately, assessment of and treatment for CVR is often performed poorly[8, 27-34] due to both patient[8, 16,32-34] and physician-related[8,16] factors and the lack of collaboration between family physicians (FP) and psychiatrists[5,32,35]. In addition, some psychiatrists lack the knowledge and competence required for diagnosing and treating CVR factors[16,32].

In the UK, an SMI register has been established. However, the monitoring of CVR for patients receiving AP without having SMI remains unaccounted for. As a result of a governmentally regulated shift from secondary to primary care, mental healthcare for patients with SMI and/or receiving AP (SMI/AP) in the Netherlands and in the UK is increasingly under the direction of FPs[36-38]. This creates an opportunity for the patients to receive CVR screening in the chronic care programs and also provides financial incentives for the FP. FPs can be of added value because CVR prevention is their daily task in high-risk patients. It also introduces the question of responsibility for the CVR screening in relation to medication use. Therefore, it is essential to increase our knowledge regarding the (somatic) care provided by FPs for these patients.

The primary aim of our study is to examine the cardiovascular risk screening practice in patients with serious mental illness or those using anti-psychotics in family practice and to identify patient characteristics that are associated with the rate of screening. We will describe a) the screening rate in SMI/AP patients without additional comorbidities, and compare this

to b) the screening rate in a group of patients who have SMI/AP and an additional reason for CVR screening: diabetes and /or known cardiovascular morbidity. The first screening rate shows the task performed by FPs for reason of SMI/AP, the latter shows what can be achieved in primary care in this patient category, despite the earlier mentioned barriers.

Methods

Study design

This study is a retrospective cohort study of patients with SMI/AP in Dutch family practice.

Study Population and Procedure

We followed the STROBE guidelines for reporting observational studies[39]. Our data were derived from a de-identified database, the Radboudumc Technology Center Health Data. This database contains Electronic Medical Records (EMRs) of family practices with information on patient demographics, diagnoses and symptoms, laboratory test results and drug prescriptions, number of visits (i.e. visits to the practice) along with characteristics of the family practices such as the number of patients registered and geographical location. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification system[40]. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC)[41]. The database provides reliable data because in the Netherlands nearly all people are registered in a family practice over a long period of time, and FPs are used to classify each visit, using the ICPC system. The FP operates as a "gatekeeper" for secondary care and consequently, medical specialists inform the FP about diagnosis and treatment[42]. However, electronic records for outpatient psychiatric visits in the Netherlands are separate from the FP's system. Therefore, visits to a psychiatrist and data concerning CVR collected there were not included. We selected patients who have an indication for yearly assessment of CVR based on their psychiatric disorder or based on the use of antipsychotic medication or lithium.

We used data from 151.238 persons, who were listed in any of the 24 involved family practices, selected by region and availability of data from our FP database, between January 2013 and December 2014. We selected patients with (I) schizophrenia, affective psychosis, bipolar disorder or psychosis not otherwise specified (NOS) with a diagnosis date prior to 1-1-

2013 or (II) at least two prescriptions of antipsychotics, or (III) a prescription of lithium, II and III prescribed for the first time before 1-7-2013. This date was chosen since we only had access to the prescription records in this defined study period. Patients were excluded if (I) aged younger than 18 years, (II) diagnosed with dementia, (III) diagnosed with delirium without the presence of a psychotic disorder, (IV) if they were not registered for more than 12 months in the selected family practice in our study period since FPs usually assess a patient's CVR profile once a year[43] and (V) diagnosed with rheumatoid arthritis, since CVR assessment in this patient category was introduced just before our study period and therefore could possibly confound our results[43,44].

Data collection

Patients with SMI/AP were divided into three groups (I) patients without another indication for yearly assessment of CVR according to the current FP guidelines[43] 'SMI/AP-only group'. (II) Patients with SMI/AP and diabetes mellitus (DM), and thus an extra indication for CVR assessment 'SMI/AP+DM group'. (III) Patients with SMI/AP and a history of a cardiovascular disease (CVD; i.e. stroke, angina pectoris, acute myocardial infarction, transient ischemic attack, intermittent claudication, and aortic aneurysm), and therefore an extra indication for CVR assessments 'SMI/AP+CVD group'. Patients with both DM and CVD at baseline were added to the SMI/AP+DM group because patients with DM are routinely part of a chronic care program that proactively invites patients for monitoring.

Our primary outcome measure was the screening rate of CVR, i.e. the proportion of patients in each subgroup that received screening for their CVR factors in the defined study period.

The CVR factors were selected as recommended in the Dutch FP guidelines (i.e. Body Mass Index (BMI), blood pressure, estimated Glomerular Filtration Rate (eGFR), smoking status, fasting glucose, lipid spectrum, use of alcohol, family history of cardiovascular disease)[43]. However, considering the observational nature of this study and the screening criteria described in previous studies[29,30], we included a broader range of assessments (Appendix A1).

We divided the observed screening into three levels: adequate, moderate, and insufficient, based on current Dutch FP guidelines[43]. The screening rate was considered 'adequate' when BMI, smoking status, blood pressure, glucose, and cholesterol/HDL ratio were all recorded at least once during the observation period since these are the assessments

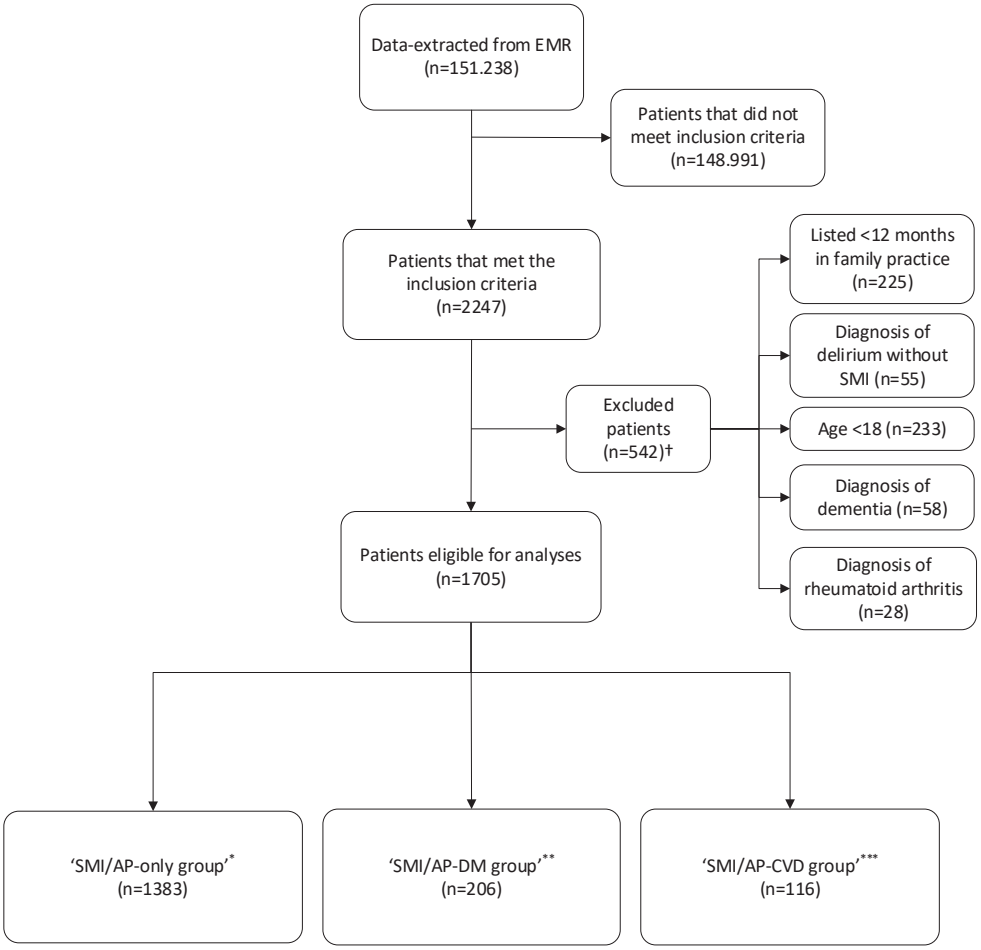
that are needed to assess the 10-year CVR of a patient and provides the indications for cardiovascular risk-lowering medication. The screening rate was considered 'moderate' when the assessment included BMI, smoking status, and blood pressure, as these can be measured without a blood test. The screening rate was considered insufficient if it did not meet these requirements. A 2-year window was chosen to gain insight into the role and awareness of the FP in this matter. Since FPs usually invite their high-risk patients once a year, patients who were screened just over the 1-year time window because of a delay in their response would be part of the unscreened group, which would underestimate the screening rate.

Moreover, we wanted to identify factors associated with any CVR screening (adequate or moderate). The following factors were studied: age, sex, type of psychiatric disease, use of antipsychotics, use of antidepressants, CVR medication (i.e. statins, blood pressure drugs, and aspirin), COPD, abuse of alcohol or drugs, any records of social issues and frequency of visits. We selected ICPC codes concerning diseases and social problems (see Appendix A2) and prescription records of antidepressants for this purpose. The ATC codes of AP, lithium, and antidepressants are listed in Appendix A3. We also selected (home) visits and calculated the frequency of visits per year for each patient.

Statistical analyses

Descriptive analyses were used to describe the patient characteristics and to provide insight in the screening rate in the three different patient groups. As a result of the hierarchical structure of the study (patients nested within practices), multilevel analyses (random intercept model) were performed that took into account the variability associated with each level of clustering. Logistic regression analysis was performed to test the differences in screening rates between the three groups. In addition, for the SMI/AP-only group, we investigated the patient characteristics from Table 1 that were associated with an adequate or moderate screening rate. First, we included characteristics for the multivariate model that were univariately associated with screening ($p < 0.20$). After that, a backward regression analysis was performed with these characteristics. A p-value of < 0.05 was considered to be statistically significant, based on two-sided tests. A sub-analysis was added to show if the results differ between two groups: patients who were included based on their diagnosis (SMI) and patients who use AP without a diagnosis that suits the use (addendum). All analyses were carried out using IBM SPSS statistics 22.0.

Figure 1. Flow chart of in- and exclusion of patients



* Patients with SMI/AP without another indication for yearly assessment of cardiovascular risk.
** SMI/AP patients with additional diabetes.
*** SMI/AP patients with additional cardiovascular morbidity without known diabetes.
† Some excluded patients fitted more than one exclusion criterion
EMR=Electronic Medical Records, SMI=Serious Mental Illness, DM=Diabetes Mellitus, CVD=Cardiovascular Disease.

Results

Of the 2247 SMI/AP patients (prevalence=1.5%), 542 patients were excluded. Figure 1 shows the flow chart of in- and exclusion of patients.

Table 1 shows the demographic and clinical characteristics of our included patients. Of these, 14.7% of patients were diagnosed with schizophrenia, 16.1% were diagnosed with an affective psychosis or bipolar disorder and 20.3% had a diagnosis of psychosis NOS. Of all 1150 patients using antipsychotics, 68.3% did not have any diagnoses concerning SMI in their medical records (n=785). Quetiapine was the most commonly prescribed antipsychotic agent (20.1%). Of included patients 27.2% had less than one visit per year, while 16.8% had over 10 visits per year. The subgroup analysis (see addendum) showed that patients with SMI more often had less than one visit while patients using AP without SMI more often had over 10 visits a year.

CVD risk factor assessment

Table 2 presents the screening rate of CVR assessment for the three SMI groups. In 8.5% of the SMI/AP-only group, risk factors were adequately assessed. Logistic regression analysis resulted in ORs for adequate screening in the SMI/AP+DM and SMI/AP+CVD groups when compared to the SMI/AP-only group of 24.6 (95% CI 17.3-35.1) and 4.2 (95% CI 2.7-6.6) respectively.

Factors contributing to screening rate

Multivariate multilevel logistic analysis showed a high frequency of visits, age, AP use, and a diagnosis of COPD were positively associated with an adequate screening rate in the SMI-only group (Table 3). SMI and AP are correlated and therefore could not be simultaneously part of the model. We chose for the variable with the most significant p-level, which was AP use.

Table 1. Comparison of patient characteristics

	SMI/AP-only group n=1383	*SMI/AP+DM group n=206*	*SMI/AP+CVD group n=116*	*Total sample n=1705*
Sex female	720 (52.1)	110 (53.4)	51 (44.0)	881 (51.7)
Mean age in years (SD)	44.9 (14.8)	58.5 (14.0)	61.8 (12.3)	47.7 (15.7)
SMI diagnosis, total	629 (45.5)	97 (47.1)	48 (41.4)	834 (48.9)
Schizophrenia	197 (14.2)	38 (18.4)	15 (12.9)	250 (14.7)
Affective Psychosis/Bipolar Disorder	217 (15.7)	34 (16.5)	24 (20.7)	275 (16.1)
Psychosis Not Otherwise Specified	307 (22.2)	28 (13.6)	11 (9.5)	346 (20.3)
SMI/AP				
SMI with AP	290 (21.0)	55 (26.7)	20 (17.2)	365 (21.4)
SMI without AP	399 (28.9)	42 (20.4)	28 (24.1)	469 (27.5)
AP without SMI	630 (45.6)	95 (46.1)	60 (51.7)	785 (46.0)
Only lithium	64 (4.6)	14 (6.8)	8 (6.9)	86 (5.1)
Medication use				
Antipsychotics, total	920 (66.5)	150 (72.8)	80 (69.0)	1150 (67.4)
Lithium	160 (11.6)	31 (15.0)	22 (19.0)	213 (12.5)
Antidepressants	558 (40.3)	91 (44.2)	58 (50)	707 (41.5)
CVR lowering medication	295 (21.3)	186 (90.3)	103 (88.8)	584 (34.3)
Comorbidity				
COPD	65 (4.7)	25 (12.1)	23 (19.8)	113 (6.6)
Alcohol abuse	68 (4.9)	19 (9.2)	12 (10.3)	99 (5.8)
Tobacco abuse	233 (16.8)	83 (40.3)	42 (36.2)	358 (21.0)
Drug abuse	101 (7.3)	3 (1.5)	2 (1.7)	106 (6.2)
Number of visits FP /year				
0	393 (28.4)	46 (22.3)	25 (21.6)	464 (27.2)
1-5	565 (40.9)	60 (29.1)	27 (23.3)	652 (38.2)
6-10	234 (16.9)	41 (19.9)	27 (23.3)	302 (17.7)
>10	191 (13.8)	59 (28.6)	37 (31.09)	287 (16.8)

Values are shown as n (%) unless otherwise noted.
SMI= Serious Mental Illness, AP=Antipsychotics, DM=Diabetes Mellitus, CVD= Cardiovascular Disease, CVR=Cardiovascular Risk, FP= Family practice, COPD=chronic obstructive pulmonary disease.

Table 2. Completeness of CVR screening for patients with SMI/AP and for subgroups with comorbid DM or CVD.

Indication for CVR assessment	*Insufficient*	*Moderate^*	*Adequate#*	*Odds ratio(95% CI)**
*SMI/AP-only group (*n=1383)	90.2 (1247)	1.4 (19)	8.5 (117)	Reference group
SMI/AP+DM group (n=206)	29.6 (61)	1.9 (4)	68.4 (141)	21.8(15.4-30.8)
SMI/AP+CVD group (n=116)	68.1 (79)	5.2 (6)	26.7 (31)	4.3(2.8-6.6)

Values are shown in %(n) unless otherwise noted.

^ BMI, smoking status and blood pressure were all recorded

BMI, smoking status, blood pressure, glucose and cholesterol/HDL ratio were all recorded.

* OR for an adequate & moderate screening rate.

CVR=Cardiovascular Risk, CI=Confidence Interval, SMI=Serious Mental Illness, AP=Antipsychotics DM=Diabetes Mellitus, CVD=Cardiovascular Disease.

Table 3. Patient characteristics associated with CVR screening for patients with SMI/AP who have no comorbid diagnosis of diabetes or CVD (n=1383).

Factor	OR	95% CI
Age	1.05	1.036-1.055
AP use +	1.62	1.20-2.18
COPD+	2.8	1.87-4.31
Number of visits FP/year*		
>10	2.24	1.65-3.03

Cardiovascular risk screening was considered to be performed if the assessment included at least BMI, smoking status, and blood pressure.

All significant variables identified by logistic regression analysis ($p<0.05$) were included in this backward stepwise regression procedure.

*Reference is ≤10 visits FP/year.

OR=Odds Ratio, CI=Confidence Interval, AP=antipsychotics, COPD=Chronic Obstructive Pulmonary Disease, FP=family practice.

Discussion

Summary

Adequate screening for cardiovascular risk by FPs in patients with SMI/AP is very low (8.5%). In patients with additional comorbidity that require screening for CVR, this was considerably higher, especially in patients with type 2 diabetes (68.4%). Screening increased with age, advancing number of visits, AP use, and the presence of COPD. It was striking that in the majority of patients using AP, a diagnosis of SMI was not recorded in the EMR.

Comparison with existing literature

The large group of AP users without an SMI diagnosis may indicate that patients use AP off-label. However, a part of this group consists of patients whose FP lacked information about the precise psychiatric disease or did not use the correct code. In addition, there are a few on-label indications for non-psychotic diseases, such as Quetiapine for unipolar, therapy-resistant depression. Other studies endorse the possibility of a high prevalence of off-label AP use[20, 45-47].

The screening rate for CVR in patients with SMI/AP has been evaluated in several studies in different countries, resulting in a wide range of screening rates[27,29,31,34,48,49]. This variation can be explained by differences in study population and methods and provides insights in factors to take into account when an intervention is considered. A study among patients in a US Medicaid program with newly prescribed AP found that 79.6% of the patients without DM were tested on glucose (non-fasting tests included) and 41.2 % on lipids[34]. Failure to receive metabolic testing was most strongly associated with younger age, fewer chronic conditions, and frequency of health care utilization regardless of the care setting (mental health care or primary care)[34]. Mangurian found that 73% of patients with SMI and DM were adequately tested in a two years' time frame. This result is comparable with ours despite our broad inclusion of patients with SMI and those taking AP without SMI[48]. A Canadian study among patients from a community health center specialized in patients with barriers to the healthcare system found adequate screening rates in over 70% of patients with SMI (n=106)[49].

Intervention studies to improve the screening rate focused on financial compensation or organizational changes. A primary care study in the UK showed that financial compensation for the task alone without organizational embedding is not enough. In this period of time, in

the UK every primary care center received payment to provide care for patients with chronic conditions, including SMI, but only just over a fifth of patients with SMI received a full CVD screening, compared with 96% of patients with diabetes (OR = 90.4; 95% CI = 64.5–126.6, p < 0.01)(31). Organizational changes are more promising. A large systematic review concluded that the presence and implementation of standard screening protocols, that were triggered by a diagnosis of SMI, may be promising avenues to ensure adequate diagnosis and screening of CVR assessment in patients with SMI[27].

The patients in our SMI/AP+DM group take part in a guideline-based integrated chronic care program due to having diabetes, resulting in almost 70% adequate screening. Although 'high', this is much lower than the screening rate for all patients with type 2 diabetes as a whole, exceeding 95%[50]. The National Diabetes Association (UK) reports on the proportion of people receiving the eight recommended care processes no difference between people with type 2 diabetes and SMI compared to people with type 2 diabetes alone (2016-2017)[51].

Strengths and limitations

The main strength of our study is the size of the study sample and the broad inclusion of patients, based on diagnoses or on prescriptions of AP, which resulted in a realistic overview of the amount of psychiatric patients with an increased CVR in primary care. We therefore think the diversity of our study group is representative of primary care patients in daily practice in the Netherlands, which contributes to the validity and reliability of our findings.

Several limitations need to be mentioned as well. First, we studied whether or not FPs screened patients with SMI/AP on CVR. The retrospective design offers limited insight into their motives. Second, we did not have access to patient records in mental health institutions, since we only used the EMRs from FPs. Consequently, it is imaginable that CVR was assessed in mental health care institutions and that our results are an underestimation of CVR screening. About half of the patients with SMI receive (additional) care from such institutions[52]. Third, it is important to keep in mind that by excluding patients who were listed for less than 12 months in family practice (n=225, 10% of all patients) there is a potential selection bias. Patients who switch FPs regularly might be homeless, uninsured, or move frequently and consequently might not be screened at all. Their absence in our study can result in an overestimation of CVR screening. Fourth, we think the small number of patients with abuse of alcohol and drugs is due to a lack of capturing these data in the EMR of the FP.

Therefore, the expected inverse relation with adequate screening could not be proven nor rejected.

Conclusions

CVR screening of patients with SMI/AP poses a challenge.

FPs have a key position in the screening for CVR and an increasing role in the care of SMI patients. We recommend that FPs accurately record psychiatric diagnoses and be vigilant with off-label prescriptions. Standardized protocols to increase the involvement of FPs create an opportunity to improve cardiovascular screening and re-evaluate AP use in patients without SMI diagnosis. Future studies should provide information concerning the best ingredients of a family physicians` chronic care program for patients with SMI/AP to improve their care.

List of abbreviations

SMI=serious mental illness; AP=antipsychotics; SMI/AP=SMI and/or AP; CVR=cardiovascular risk; DM=type 2 diabetes mellitus; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; EMR=Electronic Medical Records; FP=family practitioner; ICPC=International Classification of Primary Care; ATC=Anatomical Therapeutic drug Chemical classification; COPD=chronic obstructive pulmonary disease

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Additional file 1

Appendix A1- Included diagnostic assays

Preferred assay	**Also included**
BMI	Body weight, length, waist circumference
Systolic blood pressure	Diastolic blood pressure
eGFR	Creatinine, albuminuria, albumin/creatinine
Smoking status	
Fasting glucose	Non-fasting glucose, HbA1c
Total cholesterol/HDL ratio	LDL, total cholesterol, HDL, triglycerides
Use of alcohol	
Family history of cardiovascular disease	
Physical activity	
Dietary Intake	

Appendix A2- ICPC codes

Description or Diagnosis	**ICPC code**
Psychological diseases	
Schizophrenia	P72, P72.01
Affective psychosis, bipolar disorder	P73, P73.02
Psychosis NOS/other	P98
Dementia	P70, P70.01, P70.02
Delirium tremens	P15.02
Organic psychosis	P71, P71.04
Chronic alcohol abuse	P15, P15.01, 15.03, P15.05, P15.06
Acute alcohol abuse	P16
Tobacco abuse	P17
Medication abuse	P18
Drug abuse	P19, P19.01, P19.02

Cardiovascular diseases	
Stroke	K90, K90.01, K90.02, K90.03
Ischemic heart disease w. angina	K74, K74.01, K74.02
Acute Myocardial Infarction	K75
Ischemic heart disease w/o angina	K76, K76.01, K76.02
Transient cerebral ischemia	K89
Intermittent claudication	K92.01
Aneurysm aorta	K99.01
Diseases associated with an increased risk of cardiovascular disease or indication for yearly risk assessment	
Rheumatoid arthritis	L88, L88.01, L88.02
Diabetes Mellitus	T90, T90.01, T90.02
Chronic obstructive pulmonary disease	R95
Social issues	
Poverty/financial problem	Z01
Housing/neighborhood problem	Z03, Z03.01, Z03.02, Z03.03
Loneliness	Z04.03
Unemployment problem	Z06
Analphabetism	Z07.01
Social welfare problem	Z08, Z08.01, Z08.02
Health care system problem	Z10
Relationship problem with partner	Z12, Z12.01, Z12.02
Partner's behavior problem	Z13, Z13.01, Z13.02, Z13.03
Child neglect	Z16.02
Limited social function	Z28

Appendix A3- ATC codes and grouping of medication

Medicine	**ATC code**
Antipsychotics	
Chlorpromazine	N05AA01
Levomepromazine	N05AA02
Fluphenazine	N05AB02
Perphenazine	N05AB03
Periciazine	N05AC01
Haloperidol	N05AD01
Pipamperone	N05AD05
Bromperidol	N05AD06
Sertindole	N05AE03
Flupentixol	N05AF01
Chlorprothixene	N05AF03
Zuclopenthixol	N05AF05
Fluspirilene	N05AG01
Pimozide	N05AG02
Penfluridol	N05AG03
Clozapine	N05AH02
Olanzapine	N05AH03
Quetiapine	N05AH04
Sulpiride	N05AL01
Tiapride	N05AL03
Lithium	N05AN01
Risperidone	N05AX08
Aripiprazole	N05AX12
Paliperidone	N05AX13
Antidepressants	N06A

Additional file 2

In this addendum, we analyzed whether our results differed between two groups: patients with a SMI diagnosis and patients who use AP without a SMI diagnosis. We compared the patient characteristics between these two groups (Table A1), assessed the completeness of their CVR screenings (Table A2), and explored the factors associated with adequate screening (Table A3) separately for these two groups.

Table A1. Comparison of patient characteristics between the patients with SMI and the patients using AP without a recorded SMI diagnosis.

	Patients with SMI (n = 689)	*Patients using AP without recorded SMI (n = 630)*	*P-value*
Mean age, years (SD)	43 (14.5)	44 (14.7)	0.34
Sex, female	323 (46.9)	359 (57.0)	<0.001*
Antidepressants	140 (20.3)	381 (60.5)	<0.001*
CVR-lowering medication	126 (18.3)	146 (23.2)	0.028*
COPD	23 (3.3)	35 (5.6)	0.05*
Alcohol abuse	37 (5.4)	29 (4.6)	0.52
Smoker	102 (14.8)	125 (19.8)	0.02*
Drug abuse	55 (8.0)	45 (7.1)	0.56
Number of FP visits/year			<0.001*
0	221 (32.1)	156 (24.8)	
1–5	288 (41.8)	245 (38.9)	
6–10	107 (15.5)	118 (18.7)	
>10	73 (10.6)	111 (17.6)	

Values are shown as n (%) unless otherwise noted. *Statistical significance p value ≤ 0.05

SMI: serious mental illness; AP: antipsychotics; CVR: cardiovascular risk; COPD: chronic obstructive pulmonary disease; FP: family practice.

Table A1 shows that the two groups differ in several aspects. The percentages of women, patients taking antidepressants or CVR-lowering medication, patients with a diagnosis of COPD, and patients who use tobacco, as well as the number of FP visits, are all significantly lower in the group of patients with SMI than in the group of patients using AP without a recorded SMI diagnosis.

Table A2. Completeness of CVR screening for patients with SMI and for patients using AP without a recorded SMI, and for subgroups with comorbid DM or CVD.

Indication for CVR assessment	*Insufficient*	*Moderate^/Adequate#*	*Odds ratio (95%CI)**
SMI (n = 689)	92.7 (639)	7.3 (50)	Reference group
SMI+DM (n = 97)	39.2 (38)	60.8 (59)	19.8 (12.1–32.7)
SMI+CVD (n = 48)	72.9 (35)	27.1 (13)	4.7 (2.4–9.5)
AP use without SMI (n = 630)	88.1 (555)	9.7 (61)	Reference group
AP+DM (n = 95)	22.1 (21)	77.9 (74)	26.1 (15.2–44.8)
AP+CVD (n = 60)	65.0 (39)	35.0 (21)	4.0 (2.2–7.1)

Values are shown in % (n) unless otherwise noted.

^ BMI, smoking status, and blood pressure were all recorded (CVR screening without the need of a blood sample).

BMI, smoking status, blood pressure, glucose, and cholesterol/HDL ratio were all recorded.

* Odds ratio for an adequate and moderate screening rate.

CVR: cardiovascular risk; CI: confidence interval; SMI: serious mental illness; AP: antipsychotics; DM: diabetes mellitus; CVD: cardiovascular disease.

Table A2 reveals that the rate of adequate CVR screening by FPs is very low in both groups (7.3% for the group of patients with SMI, 9.7% for the group of patients using AP without SMI, and 8.5% for both groups combined). In patients with comorbidity that requires CVR screening, the rate of adequate screening was considerably higher, especially in patients with type 2 diabetes (60.8%, 77.9%, and 68.4% for the SMI group, the AP group, and both groups combined, respectively). A comparison between Table 2 of the main article (OR=21.8 and 4.3, respectively, for SMI/AP+DM and SMI/AP+CVD) and Table A2 in this Addendum (OR=19.8 and 4.7 for SMI+DM and SMI+CVD, respectively, and 26.1 and 4.0 for AP without SMI but with DM

or CVD, respectively) shows that the OR of the rate of screening was only slightly affected by the division of the SMI/AP group of patients into separate groups. These results therefore support the conclusion of the main article, which states that the rate of adequate CVR screening by FPs in patients with SMI or those using AP is very low, whereas patients with additional comorbidities that require CVR screening have a considerably higher screening rate.

Table A3. Factors most associated with CVR screening for patients with SMI and patients using AP without a recorded SMI diagnosis who have no comorbid diagnosis of diabetes or CVD.

Group	*Factor*	*OR*	*95% CI*
SMI	Age	1.04	1.02–1.06
SMI	COPD present	5.62	2.12–14.94
SMI	Number of FP visits/year*		
	>10	3.65	1.83–7.28
AP without SMI	Age	1.04	1.02–1.06
AP without SMI	COPD present	2.36	1.05–5.29
AP without SMI	Number of FP visits/year*		
	>10	1.89	1.07–3.37

Cardiovascular risk screening was considered to be adequately performed if the assessment included at least BMI, smoking status, and blood pressure.

All significant variables identified using the logistic regression analysis ($p < 0.05$) were included in this backwards stepwise regression procedure.

*Reference is 0 FP visits/year

OR: odds ratio; CI: confidence interval; AP: antipsychotics; COPD: chronic obstructive pulmonary disease.

The ORs of the factors age, COPD, and >10 FP visits/year shown in Table A3 are comparable with those in Table 3 of the main article (respectively, 1.05; 2.8; 2.24). This suggests that it is valid to combine the patients with SMI group with the patients using AP without SMI.

Chapter 4

Cardiovascular risk management in patients with severe mental illness or taking antipsychotics: a qualitative study on barriers and facilitators among Dutch general practitioners

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Abstract

Background

Patients with severe mental illness (SMI) or receiving treatment with antipsychotics (APs) have an increased risk of cardiovascular disease. Cardiovascular risk management (CVRM) increasingly depends on general practitioners (GPs) because of the shift of mental healthcare from secondary to primary care and the surge of off-label AP prescriptions. Nevertheless, the uptake of patients with SMI/APs in CVRM programs in Dutch primary care is low.

Objectives

To explore which barriers and facilitators GPs foresee when including and treating patients with SMI or using APs in an existing CVRM program.

Methods

In 2019 we conducted a qualitative study among 13 Dutch GPs. During individual in-depth, semi-structured interviews a computer-generated list of eligible patients who lacked annual cardiovascular risk (CVR) screening guided the interview. Data were analyzed thematically.

Results

The main barriers identified were: (i) underestimation of patient CVR and ambivalence to apply risk-lowering strategies such as smoking cessation, (ii) disproportionate burden on GPs in deprived areas, (iii) poor information exchange between GPs and psychiatrists, and (iv) skepticism about patient compliance, especially those with more complex conditions. The main facilitators included: (i) support of GPs through the use of a computer-generated list of eligible patients and (ii) involvement of family or carers.

Conclusion

This study displays a range of barriers and facilitators anticipated by GPs. These indicate the preconditions required to remove barriers and to facilitate GPs, namely adequate recommendations in practice guidelines, improved consultation opportunities with psychiatrists, practical advice to support patient adherence, and incentives for practices in deprived areas.

Key messages:

- Implementation of CVRM in patients with SMI by GPs may be hindered by a lack of knowledge about the additional cardiovascular risk, stigma towards this patient group, and a high workload.

- A supportive list of eligible patients, and support by psychiatrists and caregivers may facilitate GPs with the implementation.

Introduction

A meta-analysis of 92 studies revealed that people with mental disorders have an elevated cardiovascular risk (CVR)[1]. Patients with a severe mental illness (SMI), including schizophrenia, bipolar disorder, and non-organic psychosis, had the highest risk[1]. A Dutch study showed the all-cause mortality rate was four to five times higher in people with SMI than in the general population, mostly as a result of cardiovascular mortality[2]. The high CVR in patients with SMI may be related to stress, an unhealthy lifestyle, addictions, and distance to healthcare[3,4]. Another important factor in this elevated risk is the adverse metabolic effects of taking atypical antipsychotic (AP) medications[5]. The European guideline on cardiovascular disease prevention, which was updated after our study was completed, recommends intensified attention and support to improve adherence to lifestyle changes and drug treatment for these patients[6].

The global rates of CVR management (CVRM) remain low in patients with SMI or those using APs, which suggests an undertreatment of CVR in these patients[7,8]. In the Netherlands, the prevalence of patients with SMI and those who use APs in the Netherlands is estimated at 1,5%[8]. GPs are increasingly responsible for CVRM in patients with SMI or who use APs as a result of the governmentally generated shift of mental healthcare from secondary to primary care[9,10], as well as the growing number of off-label prescriptions of APs either initiated or continued by the GP[11]. Approximately 40–75% of current AP prescriptions are for off-label uses, in particular for anxiety and insomnia[11]. Both patients and GPs with expertise in mental health issues believe that CVRM should be delivered by the GP rather than psychiatrists[12,13].

Dutch GPs are well organized in so-called “primary care co-operatives”, which aim to improve chronic disease management for patients with diabetes mellitus, cardiovascular diseases, or high CVR[14]. GPs delegate chronic disease management to specialized nurses who help patients improve their lifestyle and provide CVR-lowering medication. In this system, patients are proactively invited for a check-up at least yearly. The inclusion of patients is based on risk categories in the multidisciplinary CVRM guideline, which does not specifically mention

patients with SMI or those taking Aps[15]. Due to a regional agreement with the health insurance companies, GPs connected to a co-operative in the eastern part of the Netherlands can include all patients with SMI or using APs in the chronic disease management program; however, four years after the initiation of this agreement, the attendance of this patient group remains low.

Previous studies explored the low rates of CVR screening for patients with SMI or using APs. First, guidelines are ambivalent about whose role it is to screen and optimize CVR[12]. Second, healthcare professionals are inconsistent in their approach and sometimes have negative perceptions about psychiatric patients, particularly regarding smoking cessation[16,17]. Third, patient access to primary care is hindered by limited help-seeking behavior, psychological barriers, and poor understanding of preventing physical illness[17]. These studies were chiefly conducted through questionnaires or focus groups among healthcare professionals, family members, or patients, and were performed in countries with different healthcare systems, often before the implementation of chronic disease management programs in primary care. The process of proactively inviting patients for CVRM in primary care starts with the GPs' willingness to do so. It is therefore important to gain insight into the views of GPs. We aimed to explore which barriers and facilitators GPs perceive when including and treating patients with SMI or using APs in an existing CVRM program.

Methods

Study design

We performed a qualitative study based on interviews with GPs about their views on and experiences with CVRM in patients with SMI or AP use. We used in-depth, face-to-face, semi-structured interviews to examine the scope of the factors involved. To identify these factors, we started every interview with an open approach followed by a phase where we used an interview guide (see Supplementary 1) based on the Consolidated Framework Implementation Research (CFIR) model[18]. This framework includes the following domains: intervention characteristics, characteristics of individuals, inner and outer settings of the general practice, and implementation process. We reported this study according to the COREQ guidelines[19].

Selection of GPs

Fourteen GPs were approached from "Onze Huisartsen", a regional primary care cooperative for chronic disease management in the eastern part of the Netherlands. In this region, local financial agreements make the CVRM program accessible for patients with SMI or AP use. We based the selection of GPs for the interviews on purposive sampling to obtain as much variation in GP experiences as possible. The research group (all authors) discussed and agreed on the rationale for ten relevant characteristics of GPs and their practices as shown in Table 1, considering various characteristics that might influence the opinion of the GP, such as 'size of the organization', 'socio-economic status of patient population', and 'collaboration with different (regional) mental healthcare providers'.

Procedure

GPs were invited by telephone to join the study. All but one, who was too busy, agreed to an interview. We conducted all interviews with guidance from a list of patients registered in the GP's own practice. This list included all patients with SMI and/or those using APs who were not participating in the chronic disease management program. The list was generated from electronic medical files and included patients with the following ICPC codes[20] P72 (schizophrenia), P73 (affective psychoses), P73.02 (bipolar disorder), and P98 (non-specific psychoses), and the ATC code[21] N05A (unless prescribed for dementia or delirium).

The GPs used the list during the interview as a tool to conceptualize what might be facilitators and barriers, using their professional knowledge and general experiences, without revealing privacy-sensitive data. We started the interviews with an open, inductive approach to give GPs ample opportunity to bring up factors they considered important. This phase in the interview was supported by the list with patients. Our interview guide was deductively composed with the elements of the CFIR framework and was used in the last phase of the interview. Often the GPs would go back to the list in this phase too, to illustrate their answers. We estimated 10–11 interviews would be needed to identify the scope of relevant factors, and from there we planned two additional interviews until no new factors were found and saturation was achieved.

Interviews

Either one researcher (KJ or LL) or both conducted the interviews between April 2019 and October 2019 in the setting of the general practice. The interviews lasted between 30 and 60 minutes. The researchers are female, had prior training in qualitative methodology, and tended to approach the participants with an open unjudgmental attitude. Researcher KJ is a GP and works for the participating primary care co-operative as a medical advisor on cardiovascular diseases. Researcher LL is a master's student. The data analysis started after the first five interviews, and from there the data collection and analysis were alternated. Thus, questions that emerged during the analysis could be addressed in the following interviews.

Data analysis

We digitally recorded all interviews, transcribed them, and imported them into Atlas.ti8 for further analysis. Thematic analysis, as described by Braun and Clarke[22], was chosen because we aimed to display the whole range of motivations, experiences, and meanings of different GPs and to argue what should be considered if GPs are asked to include and treat patients with SMI or APs in the CVRM program. The analysis was performed as follows: (1) repeated review of the transcripts to gain insights into the contents(KJ and LL), (2) independent open coding of the transcripts (KJ and LL), (3) discussion of codes to identify the underlying ideas or assumptions(all), and (4) merging codes from categories into themes reflecting the barriers and facilitators. Concepts of themes were refined by going back and forth through the data. This process of refinement was used to provide a clear sense of the scope and diversity of each theme. The research group had extensive discussions about the content of the themes and categories. The research group discussed the data in fortnightly meetings to improve the validity, and all agreed on the final categories and themes.

Societal and ethical justification

This study was conducted according to Dutch legislation on privacy and the declaration of Helsinki. There were no conflicts of interest. Ethical approval for this study was asked for but not considered necessary by the local Medical Research Ethics Committee Arnhem/Nijmegen (file number 2019-5186). We audio-recorded the verbally obtained informed consent from all GPs and their interviews were pseudonymized.

Results

The characteristics of the thirteen GPs who participated in the interviews are shown in Table 1.

Table 1: Characteristics of participating GPs (n=13)

Axis of diversity	Participants	n
Gender	Male Female	6 7
Age	Age ≤ 45 Age > 45	5 8
Association with university/GP training	Academic practice Non-academic practice	7 6
Size of organization	≤ 10 employees >10 employees	8 5
Location of organization	Rural Urban Combined	4 6 3
Socioeconomic status (SES) of the patient population	SES lower than average SES average or higher	6 7
Proportion of elderly in patient population	Elderly population higher than average Elderly population average or lower	5 8
Collaboration with different mental healthcare providers	Main collaboration with provider X Main collaboration with provider Y Main collaboration with provider Z	8 3 2
Semi-institutionalized patients registered in the practice	Yes No	6 7
Proportion of new migrants (raised abroad) in patient population	New migrant population higher than average New migrant population average or lower	6 7

Our analysis resulted in four themes and 12 categories (see supplement figure 1). The findings are presented in relation to the four themes and are illustrated by quotes. An overview of the main barriers and facilitators for each theme is shown in Table 2.

Table 2: Barriers and facilitators for each theme

Barrier	Facilitator	Theme
Lack of knowledge about additional CVR	Guideline adjustment and education	Professional
Lack of awareness	Set the agenda for the topic regionally	
Lack of knowledge about APs	Publications in medical journals about the topic	
Reactive rather than proactive approach	Feeling responsible for the patients' health	
Experienced workload	Preventive care is part of primary care	
Lack of priority / affinity for the topic		
High workload	Training for the staff	Organisation
Disproportionate burden for some practices	Use of patient list	
Problems regarding referal	Short lines of communication with psychiatrist and caregivers	Collaboration
Lack of information exchange	More awareness CVR among psychiatrists	
Low patient compliance	Involving caregiver / family	Patient
Complex patient features (addiction, low health literacy)	Doctor-patient relationship	
Risk of patients wanting to stop AP after explaining CVR		

(1) Professional

The theme 'Professional' relates to the role of the GP as an individual.

All GPs reported a lack of knowledge on how to estimate the additional risk caused by SMI or AP use. Most GPs did not consider SMI an additional risk. The use of APs, however, was recognized by the GPs as increasing the risk of cardiovascular disease.

> 'I didn't think she would qualify [for CVRM]. If she was interested, that would be fine, but I really don't think her risk is that high. She has bipolar disorder for which she has taken APs in the past. But you state that she does have a higher risk?' (GP 2)

Neither SMI nor the use of APs is mentioned in the Dutch guideline for CVRM and the CVR calculation algorithm[22]; therefore, the GPs considered CVR-lowering medication unnecessary when the calculated risk was low (green) or moderate (yellow). Additionally, smoking cessation is the most effective measure, but all participating GPs assumed that this is difficult to accomplish for patients with SMI. Moreover, they indicated that they lacked expertise on the interactions of APs with tobacco, varenicline, or bupropion.

> 'I usually explain the risks by showing the risk chart. [For a] patient [who] smokes a lot…you can tell them 'your risk is red, but don't worry, we can do something about that'. But if you show them the chart and their risk is green…you can say 'yes, your risk will be high in about 30 years', which is not very persuasive.' (GP 1)

GPs expressed varying degrees of awareness about the fact that SMI or using APs increases CVR. It was often overlooked.

> 'I think the importance [of this link] is known. You just need to make the connection at the moment of your patient's visit… With rheumatoid arthritis, this [association] is already there you see, but now the connection 'oh, SMI…[check CVR]' needs to be held at the front of the mind.' (GP 6)

GPs emphasized that they need more education about AP side effects, pharmaceutical interactions, and relevant patient factors to be able to provide personalized care for these patients. According to the GPs, it would be helpful to regularly include this topic in medical journals and regional activities like the yearly benchmark.

The intrinsic motivation of the GPs varied to providing adequate CVRM for patients with SMI or who use APs. All but two GPs provided responsive care instead of proactive care to patients with SMI or using AP; thus, these patients will only receive care if they ask for it.

> 'If we think 'oh, this calls for immediate action' then we'll do that. As doctors, we don't think in a very preventive way with these patients. We tend to act reactively.' (GP 5)

However, most GPs felt responsible for facilitating CVRM for (some) patients they recognized on the list.

> 'I want to implement [CVRM] right away because this is a group of people I feel involved with and responsible for… People with psychiatric disorders often fall through

the cracks. The fact that APs have been prescribed shows something severe is going on, or they wouldn't have had that medication. This gives us a certain responsibility.' (GP 7)

One GP admitted to feeling no affinity for psychiatry, and consequently no motivation to invite these patients to CVRM.

'For me, this is really niche. They [medical authorities] offload everything onto us. I'm not involved with this. Psychiatry is not necessarily my field of interest.' (GP 4)

Many GPs experienced a heavy workload when working with patients with mental health problems compared to other patients. The GPs in urban practices with many patients of low socioeconomic status strongly linked the high workload to the feeling of discouragement about taking up CVRM. They expressed frustration about high consultation rates and a feeling of being understaffed.

'I instantly feel tired [looking at this list of patients]. Even more work to do'. (GP 5)

Often GPs did not prioritize the invitation of patients with SMI and those taking APs to participate in CVRM programs. They were preoccupied with a variety of other topics (e.g., polypharmacy, elderly patients or renovating the practice). On the other hand, all GPs stated that preventive care is an important part of their work.

(2) Organization

The theme 'Organization' relates to the general practice organization and its policy concerning CVRM. Most GPs found the opportunity to delegate the CVRM to nurses facilitating, and some indicated that their nurses responded positively to inviting this specific group of patients.

'The nurse said, 'let's give it a try and we'll see how it goes'.' (GP 1)

Some GPs suggested that the training of the nurses would be helpful by ensuring that they are well-equipped with skills and knowledge. One GP thought his staff might not be able to cope with patients with SMI.

> 'I have a patient in mind who smells very bad…poor hygiene…lack of self-awareness. I can imagine the nurses might be reluctant and think 'what am I supposed to do here?'… They need to work one step at a time and take it slowly, with a lot of empathy. More skills might be required to achieve improvement [lower CVR] with this patient group.' (GP 10)

All GPs found the possibility of generating a list of patients with SMIs or those who use APs helpful, mainly because the list provided an overview of patients not receiving adequate care (see 'Procedure' in the Methods section). Most participating GPs needed assistance to generate it. Moreover, sometimes the list created extra work for the GPs because of errors in the electronic medical file.

GPs reported limited time as a major barrier to inviting patients with SMI or using APs to the CVRM program. The length of our participants' lists varied between 6 and 112 patients causing a disproportionate burden. The longer lists were found in practices located in deprived neighborhoods and were an important barrier in the GPs' decision on whether to invite the patients. Furthermore, with limited time, this is a task easy to postpone.

> 'You ask me why this has not been done. I think it's very simple: if it's not directly in front of me, it will remain on the to-do list.' (GP 3)

(3) Collaboration

'Collaboration' relates to the partnership between the GP, the psychiatrist, and other mental healthcare providers. The majority of GPs found patients on the list for whom they predicted CVRM would be unachievable in their practice. The GPs were (yet) unsuccessful in referring these patients to a psychiatrist. Capacity problems of mental healthcare providers result in unstable patients not receiving adequate psychiatric care, despite the best efforts of GPs. The long waiting times for mental healthcare services were often mentioned, with GPs forced to bridge this gap.

According to the GPs, complex patients are especially difficult to refer. The majority of GPs believed that mental health providers accept patients with problems suitable to the

offered therapy range. As a result, some patients with SMI who also suffer from addiction or intellectual disability are relying on the GP for care.

Shorter lines of communication with a psychiatrist can be helpful here, as mentioned by one GP.

> 'We were so frustrated with mental healthcare organization X that we contacted organization Z, which is affiliated with home care. They have a very approachable psychiatrist, who now works in our building and walks in to see if we have new referrals or fill us in on patients. They only intervene for a short period of time, until the patient is stabilized, but from there they are generally available for us if we need them.' (GP 5)

All GPs complained about not being properly informed by psychiatrists. Often, it remained unclear to them whether the psychiatrist screened for CVR; sometimes, it was even unclear if mental healthcare had been completed.

> 'Well, if the psychiatrist is involved, it makes sense that he should do [the CVRM], but in my experience they never do. In fact, they don't even ask us to do so. They don't communicate. Nothing is mentioned about CVRM at all. Organization X rarely writes a status update or even a final report to me, so I don't know whether or not they are treating my patient anymore.' (GP 8)

(4) Patient

The theme 'Patient' specifically relates to the GP's thoughts and assumptions about patient factors influencing the risks of the intervention and the compliance of patients. GPs had many assumptions about patients with SMI and how CVRM would work out for them. They often considered these patients to be noncompliant and were especially skeptical about adherence for complex patients.

GPs were generally aware of the delicate balance in the mental health of patients using AP. Some participating GPs were afraid patients might stop using AP because they had been made aware of the cardiovascular consequences.

Some GPs thought that patients would not be interested in CVRM because of the difficult circumstances in which they live. GPs noticed that problems in different areas of patients'

lives, such as poverty, substance abuse, or insecure housing, negatively influenced their motivation or capability to be compliant concerning CVRM.

> 'So if I start talking about…his cholesterol level…he will think, "What are you talking about? My GP doesn't understand my struggles".' (GP 9)

Furthermore, the GPs assumed that the patients with more complex SMI would not be able to control their lifestyle.

> 'You want the patient to be in charge and to get out more, but of course that is virtually impossible for patients with SMI.' (GP 3)

GPs suggested that printed information materials could raise patient' knowledge of their CVR and reinforce the explanation given to them.

The involvement of family or other caregivers could facilitate CVRM for patients with SMI by supporting them with appointments and their healthier lifestyle, or by revealing difficulties.

> 'Her daughter is registered in my practice too. She always comes along with her mother to appointments here. I usually know which family members are available. Maybe we should adjust this in our letter of invitation: ask them to bring a family member or carer.' (GP 10)

Finally, according to the GPs, their relationship could be used as a tool to reach patients.

> 'He is homeless. Always dodging care. But if I ask him, he will do it. Yes, I have a bond with him. He is a charming person.' (GP 7)

Discussion

Main findings

This study identified several factors that may hinder or facilitate GPs, to treat patients with SMI or using APs in a CVRM program, which were divided into four themes. The main barriers were: underestimation of CVR for patients with SMI and ambivalence to apply risk-lowering strategies such as smoking cessation and medication prescription (professional); disproportionate burdens (organization); poor information exchange between GPs and psychiatrists (collaboration); and skepticism about patient compliance, especially if their

problems are more complex (patient). The main facilitators were feeling responsible for the health of the patients, the availability of a computer-generated list of patients, low thresholds for communication with psychiatrists, and the involvement of family/carers to improve patient compliance.

Comparison with the existing literature

Implementing CVR estimation and CVR-lowering strategies in patients with SMI or using APs in the guidelines for CVRM can be beneficial. The lack of clarity in the guidelines was previously mentioned by other researchers as being an important barrier[12]. The updated European guideline now recognizes mental disorders as a risk modifier[6]. However, it still does not take into account mental disorders in the suggested risk estimation models. This is in contrast with the QRISK3 tool[23] in which the cardiovascular risk related to mental disorders is better covered. Still, balancing the positive effects of APs on mental health on the one hand, and the negative side effects on CVR on the other hand, remains a challenging task for the GP, especially when changes to prescribed APs are considered. A short line of communication with a psychiatrist is helpful for obtaining advice, as one of our participants mentioned. Previously, Bramberg suggested the introduction of a liaison physician between GPs and psychiatrists, trained in internal medicine and somatic comorbidities of SMI[24].

The skepticism of our participants about expected adherence to appointments is in line with previous research[16]. One explanation is that it is a result of underlying negative stigma towards patients with SMI. Studies demonstrate that stigma creates barriers resulting in poorer physical care[17,25]. A key strategy for stigma reduction in healthcare is contact with trained people who lived the experience of a mental illness[26]. However, expecting low adherence is realistic to some extent, as a systematic review found that mental illness, addiction, and low SES correlate significantly with not attending appointments[27]. Practical suggestions to improve compliance might help to implement CVRM. In line with other studies, some of our participants recommended involving supportive carers to improve attendance[16,24]. Other proposed strategies are the use of direct methods such as telephone invitations or home visits, which are more effective than written invitations[16].

According to our participants, the patient list, which provides an overview of patients with SMI or using APs who lack annual screening, was very helpful. In the UK, there is a

national register of people diagnosed with SMI or on lithium therapy[28]. With the use of this register, Yeomans studied the effects of a template-based health check compatible with the primary care computer system. The system was used by 75% of the practices in the test region and resulted in more accurate data recording[29]. Similar to our finding that the length of the lists varied extensively between practices, the percentage of patients who were recorded in GP registers of SMI ranged from 0.5% to 1.5% (three-fold variation) for clinical commissioning groups in England[28]. Additionally, the association of socioeconomic deprivation with mental health disorders increases the workload of practices located in deprived neighborhoods[30].

Strengths and limitations

The computer-generated list identifying suitable patients facilitates the GPs and has never, to our knowledge, previously been used as a tool during interviews with GPs. The list helped GPs to illustrate their views and enabled the researcher to reflect on these views, which reduced the risk of researcher bias. The GPs were purposively sampled, and the participation rate was very high, providing a broad and diverse spectrum of the barriers and facilitators foreseen by GPs.

Our results depend on regional policies arranged by the primary care co-operative, which impedes direct generalizability. For instance, financial barriers might dominate the results in other regions of the Netherlands. Nevertheless, our results seem relevant to other regions or countries, when planning the implementation of CVRM in patients with SMI or AP users. Furthermore, researcher KJ works for and with the GPs of the co-operative, which could have influenced their responses in the desired direction.

Implications for practice

All CVRM guidelines should acknowledge mental disorders as risk modifiers and preferably instruct on how to estimate the additional risk.

Additionally, consultation opportunities with psychiatrists should be made available. GPs need advice if adverse metabolic effects worsen and if smoking cessation is considered during AP treatment. The availability of a computer-generated list of patients is interesting to use as a

tool in interview studies. The interviewee has the opportunity to mention their own barriers and facilitators before being influenced by the researchers' questions.

Other preconditions that can be considered are support for practices in deprived areas, and organizing a stigma-reducing intervention with trained people who lived the experience of a mental illness for GPs and nurses.

Conclusion

This study displays a range of barriers and facilitators anticipated by GPs divided in four themes. These indicate the preconditions required to facilitate GP inclusion of this specific population in CVRM programs, namely adequate recommendations in practice guidelines, improved consultation opportunities with psychiatrists, practical advice to support patient adherence and incentives for practices in deprived areas. Otherwise, CVRM for patients with SMI or using AP will probably remain on many to-do lists.

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Supplements

Supplementary 1. Interview guide

The patients' list

Can you look up a few patients on the list in your medical files and indicate the main reasons why this patient was not included in the CVRM chain care? What could help facilitate the invitation of these patients for a CVRM screening?

CFIR-based questions

Intervention (of CVRM for patients on the list)

1. ***Supporting evidence*** What kind of additional information is needed about the increased CVR in patients with SMI/APs to get staff on board?

2. ***Benefits*** Does this approach have (dis)advantages over the current way care is arranged for them? If yes, which one?

3. ***Alternative*** Is there another intervention that you would rather implement? Can you describe that intervention? Why would you prefer the alternative?

4. ***Adaptability*** What changes or alterations do you think you will need to make to the intervention for it to work effectively in your setting? Do you think you will be able to make these changes? Why or why not?

5. ***Complexity*** How complicated is the intervention (inviting patients to the CVRM programme)? Please consider the following aspects of the intervention: duration, scope, intricacy and number of steps involved, and whether the intervention reflects a clear departure from previous practices

6. ***Design*** How do you find the quality of the supporting tools (patient list, invitation letter, document with regional agreements)? Do you know where to find the tools? Are they relevant? Are you missing anything?

Outer setting

7. ***Patient needs and resources*** How do you think patients respond to an invitation letter for CVRM screening? Have you heard stories about the experiences of others? Can you describe a specific story?

8. Are there characteristics of this patient group that complicate CVRM for patients with SMI/AP?

9. ***Colleagues*** Can you tell me what you know about colleagues who have implemented the intervention or other similar programmes? How has this information influenced your decision to implement the intervention?

Inner setting

10. ***Practice organisation*** How will your practice's infrastructure influence the intervention's implementation (practical implementation, maturity of the organisation, scope, current CVRM programme)? How will the infrastructure facilitate/hinder the intervention's implementation?

11. ***Changes*** What kinds of infrastructure changes will be needed to accommodate the intervention? Changes in scope of practice? Changes in formal policies? Changes in information systems or electronic records systems? Other?

12. ***Meetings*** Are meetings, such as staff meetings, held regularly? Who typically attends? How often are the meetings held?

13. ***Culture*** To what extent are new ideas embraced and used to improve your organisation? Can you describe a recent improvement project?

14. ***Tension for change*** How essential is this intervention to meet the needs of the patients in your practice? How do people (including yourself) feel about current practice?

15. ***Compatibility*** Does CVRM for patients with SMI/AP fit with existing work processes? What are likely issues or complications that may arise? Will the intervention replace or complement a current programme or process? In which ways?

16. ***Priority*** Do you have ongoing projects with a high priority? What is the priority of getting the intervention implemented relative to other initiatives that are happening now?

17. ***Goals*** How does the implementation of the intervention align with other organisational goals?

19. ***Learning climate*** Can you describe a recent innovation in practice, including the motivation, milestones achieved, helping factors, key players, and your involvement? Were people happy with the outcome? To what extent do you feel like you can try new things to improve your work processes?

20. ***Resources*** Do you expect sufficient resources to implement and administer the intervention? If yes, what resources are you counting on? Are there any other resources you received or would have liked to receive? If no, what resources are not available?

Individual

21. ***Knowledge*** What do you know about CVRM for patients with SMI/AP or its implementation?

22. ***Beliefs*** How do you feel about the intervention used in your practice (stress, enthusiasm) and why?) How do you think things are going now?

23. ***Confidence*** How confident are you that you can implement the intervention successfully? What gives you that level of confidence (or lack of confidence)?

24. ***Internships of change*** (Show figure of Prochaska's stages of change) Which phase represents your situation regarding the implementation of CVRM for patients with SMI or using AP?

Process

25. ***Planning*** Can you describe the plan for implementing CVRM for patients with SMI/AP? How detailed and realistic is it? Who knows about it? What is the division of tasks? What do those involved think of their role? Who is the leader?

26. ***Champions*** Other than the formal implementation leader, are there people in your organisation likely to champion (go above and beyond what might be expected) the intervention?

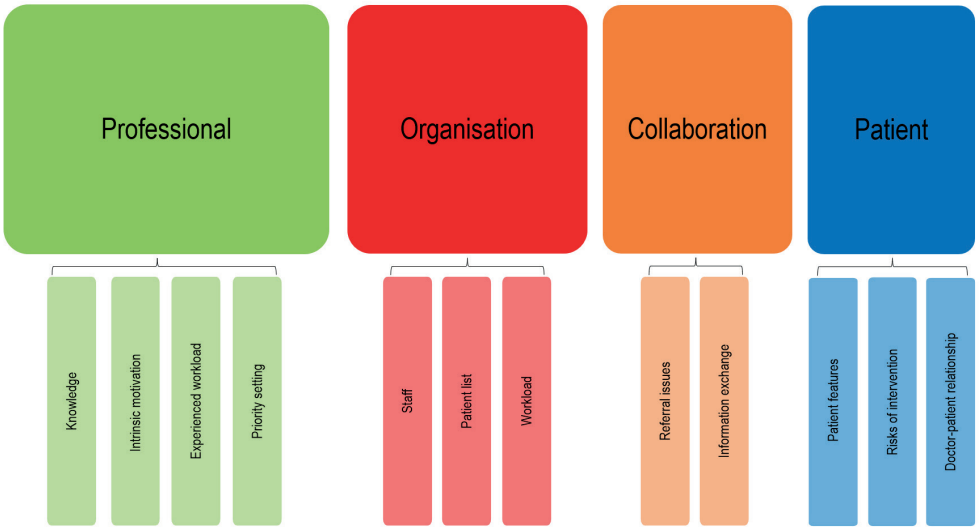
27. ***Key Stakeholders*** What steps have been taken to encourage individuals to commit to using the intervention? Who could need that?

28. ***Inviting patients*** Are you considering inviting patients to the CVRM programme differently?

Overall

29. ***Advice*** Do you have any additional remarks? Would you recommend this intervention?

Supplement Figure 1. Presentation of themes and categories



Chapter 5

Transmural collaborative care model for the review of antipsychotics: a feasibility study of a complex intervention

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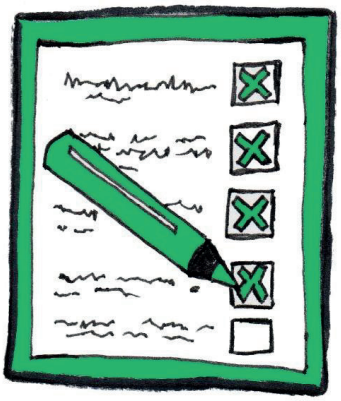


Abstract

General practitioners (GPs) are often unaware of antipsychotic (AP)-induced cardiovascular risk (CVR) and therefore patients using atypical APs are not systematically monitored. We evaluated the feasibility of a complex intervention designed to review the use of APs and advise on CVR-lowering strategies in a transmural collaboration. A mixed methods prospective cohort study in three general practices in the Netherlands was conducted in 2021. The intervention comprised three steps: a digital information meeting, a multidisciplinary meeting, and a shared decision-making visit to the GP. We assessed patient recruitment and retention rates, advice given and adopted, and CVR with QRISK3 score and mental state with MHI-5 at baseline and three months post-intervention. GPs invited 57 of 146 eligible patients (39%), of whom 28 (19%) participated. The intervention was completed by 23 (82%) and follow-up by 18 participants (64%). At the multidisciplinary meeting, 22 (78%) patients were advised to change AP use. Other advice concerned medication (other than APs), lifestyle, monitoring, and psychotherapy. At 3 months post-intervention, 41% (28/68) of this advice was adopted. Our findings suggest that this complex intervention is feasible for evaluating health improvement in patients using AP in a trial.

Introduction

Care for patients using antipsychotics (APs) is complex, and general practitioners (GPs) have become increasingly involved in this care. They participate in a growing trend of initiating APs off-label, e.g. for anxiety, personality disorders, or sleeping problems[1-4]. In 55% of the cases in the Netherlands, APs are prescribed by GPs[5].

Mainly atypical APs have been shown to increase cardiovascular risk (CVR)[6,7]. Patients using APs should be monitored at least annually to find and treat adverse effects according to international guidelines[8-11]. In many countries, such as the UK and the Netherlands, in primary care, chronic disease management programs have been developed for CVR management (CVRM)[12,13]. In these programs, trained nurses help patients to reduce CVR with lifestyle interventions and medication.

However, patients on APs are rarely included in CVRM programs[14,15]. In our earlier study, examining the facilitators and barriers for CVRM for patients with severe mental illness (SMI) and/or APs, GPs mentioned several barriers, including a lack of awareness of the

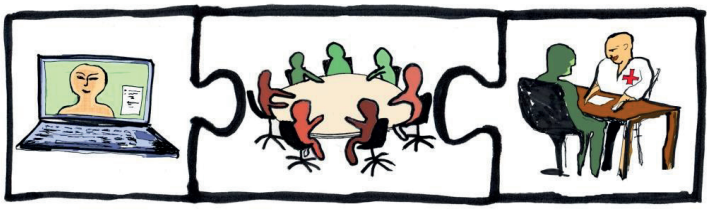
elevated risk, reluctance to invite these patients to their program as this could be complicated and time-consuming, and low expectations on the capability of these patients to develop a healthy lifestyle[14]. GPs stated that they feel responsible for their patient's health, but that changes to the APs should be the responsibility of the psychiatrist[14].

Papers about the efficacy of interventions to lower the CVR of patients with SMI and/or APs in primary care are scarce. Only one comprehensive trial, Primrose, studied this among patients with an SMI, high levels of cholesterol, and one other risk factor[16] but found no difference in total cholesterol level at 12 months follow-up.

We think that a transmural intervention in which the GP is supported by a psychiatrist in considering specific AP side effects and interactions can raise the efficacy. For instance, dose reduction and switching to an AP drug with a better metabolic profile are promising strategies to lower CVR. The intervention must help to overcome the barriers mentioned by GPs and address relevant patient factors, which may hinder the required personalization of CVRM.

To tailor care to patients' specific needs, a complex intervention was developed by a regional transmural task force consisting of relevant stakeholders, e.g. GPs, psychiatrists, nurses, people with lived experience, and pharmacists (see project description and figure S1 in the supplements)[17]. This intervention is called '**T**ransmural collaborative care model for CVRM and medication review for patients using **A**ntipsy**C**ho**TIC**s (TACTIC)' (Fig. 1). After completing TACTIC, both patients and professionals are better prepared to follow the regular CVRM program in the general practice.

Figure 1. *The TACTIC intervention consists of a webinar, a multidisciplinary meeting, and a shared decision-making visit.*



Authors of a recently published review reported a paucity of papers on conducting AP medication reviews in primary care[18]. TACTIC meets the recommendations made by the authors for such an intervention: to foster conversations between GPs and patients, to increase knowledge regarding AP treatment, and to enable appropriate and safe prescribing[18].

TACTIC is a complex intervention, as defined by the British Medical Research Council[19], and, therefore, conducting a mixed methods feasibility study before conducting a trial is recommended. The results of a comprehensive qualitative study will be reported separately. If proven feasible, the potential effects of TACTIC on CVR and mental health in patients using APs will be studied in a future stepped-wedge cluster randomized controlled trial, which has been planned for 2023 and 2024 (clinicaltrials.gov NCT05647980). The main objective of this quantitative feasibility study was to evaluate the delivery of TACTIC, including recruitment and retention of subjects. Secondary objectives were to outline the baseline characteristics of this patient group; to explore the numbers and types of advice given regarding the use of APs and CVR during the multidisciplinary meetings; and a preliminary examination of the effectiveness.

Methods

Ethics

Ethical approval for this study was waived by the local Medical Research Ethics Committee Arnhem/Nijmegen (file number 2020-7240). This study was conducted according to Dutch legislation on privacy and the Declaration of Helsinki. All patients were properly informed and gave written informed consent.

Study design

In 2021, we conducted a prospective cohort feasibility study in which we implemented the TACTIC intervention in three Dutch general practices and followed participants for 3 months after they received the intervention. Reporting is in line with the CONSORT extension for randomized pilot and feasibility trials[20,21].

Setting

Three practices were approached and agreed to participate. These practices are members of the primary care cooperative 'Onze Huisartsen', located in the Eastern part of the Netherlands, which united 105 general practices with 385,408 registered patients at the time of the study. Of these patients, 4,045 (1.05%) were ≥25 years of age and used APs.

Table 1. *In- and exclusion criteria.*

Inclusion criteria	- Chronic use of AAPs, defined as ≥3 prescriptions or ≥2 repeat prescriptions or a label for chronic use. The ATC codes* are similar to those in the QRISK3 algorithm as far as they are registered in the Netherlands: N05AX12, N05AD06, N05AH02, N05AE05, N05AH03, N05AX13, N05AH04, N05AX08, N05AE03, N05AX15, N05AX16 - Under care of the GP for mental disorder. First, this was defined as "not under care of a psychiatrist" based on the lack of correspondence in the patient's electronic medical record in the past 12 months. However, it appeared that correspondence was often missing even though the patient was still seeing a psychiatrist. Therefore, we changed the definition to: "the GP authorized the renewal of AAP prescriptions" and is therefore responsible for monitoring the pros and cons.
Exclusion criteria	- Age <25 or >84 years. The QRISK3 algorithm is not validated for these age groups - A history of CVD, signaled by the ICPC codes** K74, K75, K76, K77, K90.00, K90.03, K92.01, and K99.01. QRISK3 can only be used for patients without CVD - A diagnosis of delirium or dementia (ICPC codes** P15.02, P70 or P71). The execution of the TACTIC intervention is unsuitable for patients on AAP for these diagnoses.

*The prescriptions from the ATC codes[22].

**The diagnoses from the ICPC codes[23].

AAP, atypical antipsychotic; ATC, anatomical therapeutic chemical; CVD, cardiovascular disease; CVRM, cardiovascular risk management; GP, general practitioner; ICPC, International Classification of Primary Care; QRISK3, a tool to calculate the estimated CVD risk within the next 10 years for people (including those with type 2 diabetes) aged between 25 and 84 without CVD.

Participants

The criteria for patient inclusion and exclusion are shown in Table 1. In our future trial, we intend to assess our primary outcome CVR using the QRISK3 score (see the explanation of the QRISK3 algorithm in the 'Data analysis' section). The QRISK3 algorithm is only valid for people who do not already have a diagnosis of cardiovascular disease (CVD; coronary heart disease or stroke/transient ischemic attack). Therefore, a history of cardiovascular diseases is one of the exclusion criteria of our study.

Each GP generated a list of eligible patients based on the electronic medical records (EMRs)[24]. The list included all patients meeting the criteria as described in Table 1. To exclude patients under psychiatric care, GPs had to check for any correspondence. However, the GPs informed us that, during the process of inviting patients, many times correspondence was lacking when a psychiatrist was involved. Therefore, we changed the definition of our inclusion criterion 'Under care of the GP for mental disorder' from 'not under care of a psychiatrist' to 'the prescriber of the AP must be the GP'. After all, the prescriber is responsible for monitoring adverse effects.

We expected to include 84 eligible patients in three practices, based on the average number of AP users in Dutch general practices[25] and the number of registered patients in the participating practices. This amount is enough to evaluate the delivery of TACTIC and will show how many practices we need to include to reach the preferred sample size in our future trial.

GPs invited the selected patients by telephone in the period March to May 2021. In case patients were interested, further information about the study was sent to them by mail. Study information was tailored to readers with a low literacy level. Each patient was then called by members of the research team (KMJ or KJvdBB) to answer possible questions and check the study criteria. All patients who were willing to participate signed informed consent and were invited to their general practice for a baseline assessment before the TACTIC intervention started. Details of the baseline assessment will be described later on.

TACTIC intervention

TACTIC comprised three unique and consecutive steps (also see Fig. 1):

- Step 1. A 90-minute digital group meeting to inform patients and their close ones about the multidisciplinary meeting in Step 2. We used an online tool called

WebinarGeek, in which patients could join anonymously, chat live, and replay the recordings[26]. During the webinar, the individuals with whom the patient would interact during the multidisciplinary meeting introduced themselves and clarified their roles. This was particularly essential for the patient coach with lived experience and the nurse since patients were not aware of how they could benefit from their assistance. After the webinar, and as an extra preparation for the next step, each patient's pharmacist provided information on medication use and interactions. In the Netherlands, patients are free to choose their preferred pharmacy. However, they don't often switch pharmacies as only 1.9% of patients receive medication from a different pharmacy than the one they used in the previous year[27]. All relevant information was shared with the psychiatrist using digital consultation[24]; this included diagnoses, medication, blood pressure, body mass index (BMI), laboratory results on CVR, pharmacist medication review, results of the side effects questionnaire, and the most recent psychiatrist's letter (if available).

- Step 2. A 15-minute multidisciplinary meeting per patient. The time allotted for individual meetings was considered to be enough and an efficient use of all caregivers' time. At the meeting, the patient, a caregiver (optional), the GP, a psychiatrist, a nurse specialized in CVRM or mental health, and a patient coach with lived experience evaluated the patient's medication and CVR. The role of the coach was to underline the patient's perspective and to introduce sources of support within the community to improve their well-being[28]. The multidisciplinary meeting resulted in individualized advice on AP use (continuation, deprescribing, or switching) and reducing CVR by lifestyle strategies and possibly medication.
- Step 3. A visit to the GP in which the advice of Step 2 was used to draw up an individualized treatment plan by shared decision-making.

Three months after receiving the TACTIC intervention, all participants were invited for a follow-up visit with the nurse for measurements and to evaluate the plan.

Outcome measurements

For our main objective, i.e., to evaluate the delivery of TACTIC, including recruitment and retention of subjects, we collected the following information at three-month follow-up: The GPs manually added whether they invited each patient and reasons for non-invitations or non-

participations to an anonymized list of eligible patients that was received by the research team via secured email. After obtaining informed consent, patients visited their GP for baseline measurements (T0). Their participation in TACTIC was documented in the EMR, including dates, advice, and plans.

For our secondary objective 'to outline the baseline characteristics of this patient group' we collected from the EMR of each practice the following CVR measures: BMI, systolic blood pressure (including variability), lipid measurements, estimated glomerular filtration rate, albumin-to-creatinine ratio, and smoking status. Moreover, all actual diagnoses relevant for inclusion and exclusion and estimation of CVR, all prescriptions of the past 5 years, relevant referrals, financial records indicative of socioeconomic status (in the Netherlands, per capita rates are higher in deprived areas), and recorded advice and treatment plans concerning TACTIC were collected.

Data from questionnaires

Participants completed the following digital questionnaires at baseline (a total of 37 questions):

- Questions about smoking habits, achieved education level (low, middle, or high)[29], ethnicity, and family history of CVD.
- The Somatic Mini Scale (SMS), based on the Liverpool University Neuroleptic Side Effect Rating Scale, in which patients score 18 adverse effects of their medication on a five-point Likert scale. The score ranges from 0 to 72. This questionnaire was developed by Mental Health Services Central, a community mental health service provider in the Netherlands, and is in the process of validation. According to Mental Health Services Central, a score of 30 or higher is hazardous and should be reported to the prescriber[30].
- The Mental Health Inventory (MHI-5), a subscale of the 36-item Short-Form Health Survey, to measure mental health-related quality of life[31]. The score is between 0 and 100, and patients with a score ≥60 are considered mentally healthy.
- The EuroQol 5 dimensions 5 levels (EQ-5D-5L) questionnaire, to measure the generic quality of life[32]. These five questions were included to enable us to compute quality-adjusted life years in the future trial. The scores range from less than 0 (where 0 is the

value of a health state equivalent to death; negative values represent values as worse than death) to 1 (the value of full health).

For our secondary objective 'to conduct a preliminary analysis of the effectiveness', at the 3-month follow-up visit with the practice nurse, we collected CVR measures (T1) from the EMR. The questionnaires were repeated and supplemented with the Dutch-validated 8-item Client Satisfaction Scale (CSQ-8)[33]. The latter is recommended for use in psychiatric patients to measure patients' satisfaction with care[33]. The sum of eight sub-scores about different aspects of therapy (TACTIC) can vary between 8 and 32, with higher scores indicating greater satisfaction.

Data analysis

The data were examined using descriptive statistics. Means and standard deviations (SDs) were calculated for continuous data, and frequencies and percentages were calculated for categorical data. For the analysis of changes in the QRISK3 score, we used the Wilcoxon signed-rank test in SPSS (version 25).

QRISK3 algorithm

To assess CVR, the Dutch guideline advises using SCORE [13]. We opted for QRISK3 over SCORE because SCORE fails to take into account the extra risk that comes with an SMI or the use of APs[34], and it is not validated to evaluate the risk of patients who suffer from diabetes. For patients with diabetes, the predicament involving the use of APs is even more pressing than for those who do not have diabetes. Therefore, we used QRISK3[35], which does include diabetes and the aforementioned additional risks for this patient group. QRISK3 is designed as a screening tool. We had to make adjustments to the QRISK3 score algorithm to enable us to measure change. These adjustments are found in Table S1 in the supplements. The Townsend deprivation score (TDS) is one of the variables of the QRISK3 score. In the Netherlands, a different deprivation index is used[36,37]. In the QRISK3 score algorithm, the TDS was set to zero because we did not have this information. Additionally, we applied a revised TDS score and reported this as QRISK3_TDS. To avoid overestimation of the risk, we used the TDS value at p20 (below which are the 20% most deprived of the British population) for the 10% most deprived patients in the Dutch population, who are identified in the financial EMRs, which are

based on postal codes stratified by measuring three variables: wealth, level of education, and unemployment[38].

Additional analyses of QRISK3 score

In absolute risk assessments like QRISK3 the influence of unmodifiable CVR factors like age is high. To gather more insight about what can be gained in health improvement for this often overlooked patient group, we wanted to explore different outcome measures to show health effects for the individual rather than the mean changes. Therefore, we calculated the room for improvement for each individual (qrisk_max_achievable_reduction), which is the difference from a QRISK3 score of a person with all modifiable risk factors optimized. Furthermore, we calculated the proportional risk reduction by using this formula: (qrisk3_score_T0 - qrisk3_score_T1) / qrisk_max_achievable_reduction) * 100.

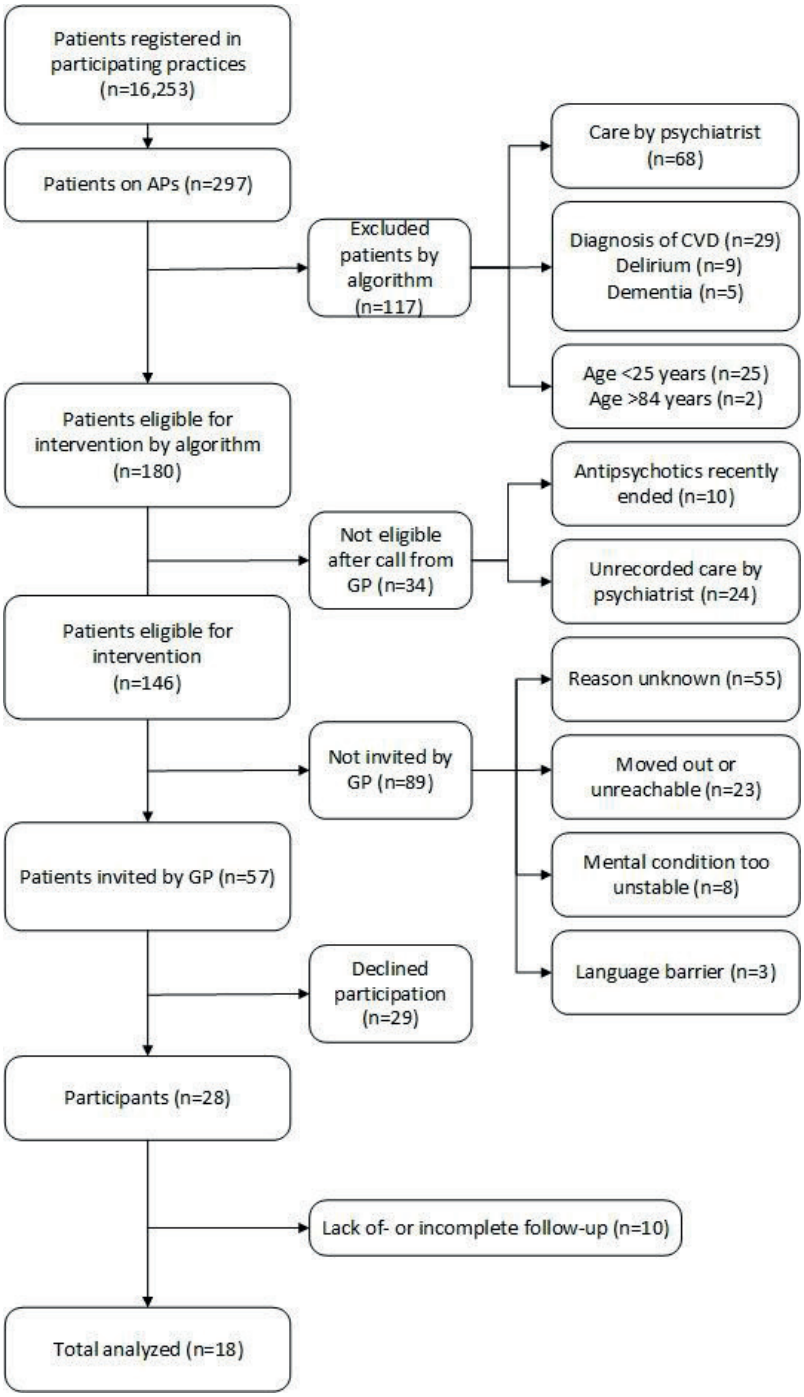
The proportional risk reduction expresses that a patient with 10% risk, who could improve to 5% has a maximum of 5% risk reduction. An improvement of 1% would be a proportional risk reduction of (1:5 *100=) 20%.

Results

Recruitment and retention of subjects

Fig. 2 shows the flow chart of included and excluded patients in the pilot practices and the GPs' reasons for exclusion resulting in 28 participants. No reason was given for approximately 61% (n=55) of eligible patients. Recruitment was between March 1 and May 1, 2021. It is noticeable that 24 patients were cared for by a psychiatrist without the knowledge of the GP. There was a lack of follow-up or it was incomplete for 36% (n= 10). The details of these cases are shown in Table 3. The dropouts were not associated with changes in AP prescriptions. The data collection ended 4 months after the last multidisciplinary meeting.

Figure 2. Flow chart of inclusion and exclusion and follow-up of patients.



AP, antipsychotic; CVD, cardiovascular disease; GP, general practitioner.

Baseline characteristics

The baseline characteristics of the participants are shown in Table 2. The mean participant age was 49 years (SD=11). The socioeconomic status was low in 35.7% of participants. The educational level was high in 37%. Quetiapine was the most commonly prescribed AP agent. Only 14% of the participants had a diagnosis of psychosis or bipolar disorder. All participants reported adverse effects. The mean score of the SMS was 22.5 (SD=10.6), which is categorized as 'high'. Nine (32%) participants scored ≥30, which is categorized as 'very high' (should be reported to the prescriber). The mean MHI-5 score was 56.8 (SD=18.01). The distribution of QRISK3 was positively skewed, as shown in Fig. 3. We did not find a statistically significant or clinically significant difference in mean QRISK3 score between the dropouts and those who had a complete follow-up (Fig. 3).

Table 2. Participant characteristics at baseline (n=28).

Demographic:	
Age in years mean (SD)	49 (11.1)
Female n (%)	13 (46.4)
Country of birth	
The Netherlands n (%)	24 (85.7)
Morocco n (%)	2 (7.1)
Other n (%)	2 (7.1)
Education*	
Low n (%)	7 (22.2)
Middle n (%)	11 (40.7)
High n (%)	10 (37.0)
Low socioeconomic status n (%)	10 (35.7)
Mental health:	
Primary psychiatric disorders	
Depressive disorder n (%)	6 (21.4)
Personality disorder n (%)	5 (17.9)
PTSD n (%)	4 (14.3)
Autistic spectrum disorder n (%)	3 (10.7)
Anxiety disorder n (%)	3 (10.7)
Bipolar disorder n (%)	2 (7.1)
Psychosis n (%)	2 (7.1)
Anorexia nervosa n (%)	1 (3.6)
ADHD n (%)	1 (3.6)
Insomnia n (%)	1 (3.6)

AP agent	
Quetiapine n (%)	16 (57.1)
Risperidone n (%)	7 (25.0)
Aripiprazole n (%)	3 (10.7)
Olanzapine n (%)	2 (7.1)
Adverse effects for APs	
Not at all	0
Very little	0
A little n (%)	3 (10.7)
Much n (%)	16 (57.2)
Very much n (%)	9 (32.1)
MHI-5 score mean (SD)	56.79 (18.01)
Quality of life:	
EQ-5D score mean (SD)	0.31 (0.28)
CVR:	
QRISK3 score mean (SD)	11.17 (14.51)
QRISK3 score with revised TDS mean (SD)	11.89 (14.85)
Smoking**	
Never n (%)	8 (28.6)
Past n (%)	10 (35.7)
Light n (%)	4 (14.3)
Medium n (%)	5 (17.9)
Heavy n (%)	1 (3.6)
Atrial fibrillation n (%)	1 (3.6)
Migraine n (%)	3 (10.7)
Chronic kidney disease, stages 3–5 n (%)	4 (14.3)
Family history of CVD n (%)	13 (46.4)
Diabetes mellitus type 2 n (%)	2 (7.1)
Chronic corticosteroids n (%)	2 (7.1)
Statins n (%)	1 (3.6)
Antihypertensive medication n (%)	4 (14.3)

*Definition of grouping according to Central Bureau voor de Statistiek (Statistics Netherlands)[29].

**Light smoker <10, moderate 10–19, heavy >19 cigarettes a day.

ADHD, attention deficit hyperactivity disorder; AP, antipsychotic; CVD, cardiovascular disease; CVR, cardiovascular risk; EQ-5D, generic quality of life; MHI, Mental Health Inventory; PTSD, post-traumatic stress disorder; QRISK, person's risk of developing a heart attack or stroke over the next 10 years; SD, standard deviation; TDS, Townsend deprivation score.

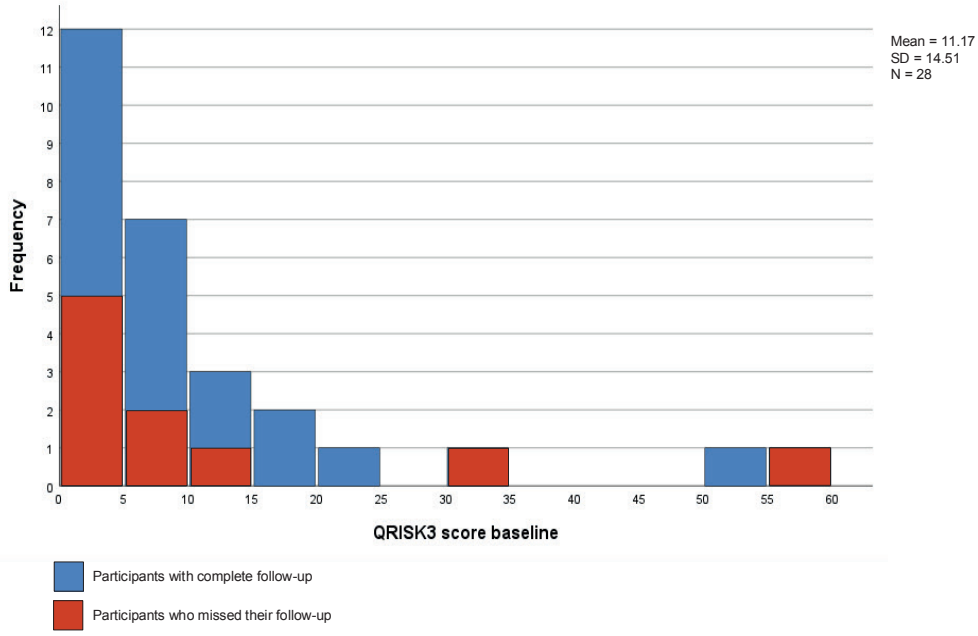
Table 3. Lack of or incomplete follow-up.

ID	Reason for drop out	Timing in relation to intervention	Advice multidisciplinary meeting	Changes in prescriptions	Diagnoses related to AP prescription
24	Dissatisfaction with step 2	Shortly after step 2	Consider lowering Abilify 15 mg in the future	Ended study therefore no further data	Bipolar disorder
12	Died of cancer	Shortly after step 2	Consider halving dosage Quetiapine	No changes	Anxiety disorder
16	Attempted suicide and admission to clinic	Shortly after step 1			Depressive disorder
27	2 admissions to hospital for dysregulation diabetes mellitus	Between step 1 and 2	Consider lowering Pregabalin	No changes	PTSD*
01	Divorced and became homeless	Between step 3 and follow-up	Due to high anxiety level, lowering Quetiapine is not appropriate. Trial treatment Topiramate 25 mg is an option. Smoking cessation	No changes Quetiapine, started Varenicline	PTSD*
11	Grandmother entered palliative stage	Between step 3 and follow-up	Smoking cessation. Lower dosage Quetiapine from 50 mg to 37.5 mg	Quetiapine was lowered from 50 mg to 25 mg, started Varenicline	Anxiety disorder, Depressive disorder, anorexia
13	4 children who had been placed under guardianship unexpectedly came back home	Between step 1 and 2	Schedule a meeting with all health workers involved	No changes	Borderline personality disorder, ADHD**, sleeping problem
22	Spouse got cancer, palliative trajectory	Between step 3 and follow-up	Risperidone from 1.0 mg to 0.5 mg or switch to Quetiapine 25 mg. If overstrung, then back to Risperidone 1mg	Risperidone was lowered from 1 mg to 0,5 mg	Autism spectrum disorder, attention deficit hyperactivity disorder

26	Left for Morocco	Between step 3 and follow-up	Quetiapine nightmares. Alternatives: Topiramate 25 mg or Mirtazapine	Tried Topiramate, not satisfactorily	Depressive disorder, sleeping problem
28	Missing	Between step 3 and follow-up	Citalopram is relatively high dosed, reduced to 30 mg in a stable period. If that goes well then reduce Olanzapine to 2.5 mg or switch to Haldol or Risperidone	No changes	Bipolar disorder

ADHD, attention deficit hyperactivity disorder; AP, antipsychotic; PTSD, post-traumatic stress disorder.

Figure 3. Distribution of QRISK3 score at baseline.



Numbers and types of advice given

The intervention was completed by 23 of 28 participants (82%). The multidisciplinary meeting (step 2) generated multiple pieces of advice per patient, based on current insights and

guidelines and taking into account the patients' wishes. Supplement Table S2 shows the type and topic of the advice and whether it was adopted. The majority of the patients were advised to change their AP use immediately or in the future (59% and 19%, respectively). After 3 months, 41% of all advice (28/68) was followed. Out of 10 smokers, eight completed the intervention. Five of eight agreed on smoking cessation during the multidisciplinary meeting and four of them had quit smoking at the follow-up visit.

The potential effectiveness of TACTIC

For participants with a complete follow-up, the QRISK3 scores at follow-up were significantly lower than at baseline (Z= –2.112, p=0.035). The table in the supplements (Table S3) displays the change in all secondary outcome variables of patients who completed follow-up. The proportional risk reduction is presented in supplements Fig. S2. The mean improvement was 25.4% (n=18, SD=58.7). The improvement on the MHI-5 score was not significant (Z=0.264, p=0.79). All changes in patient outcomes can be seen in the supplement Table S3. The patients' satisfaction with the intervention was slightly above neutral (n=21, mean CSQ-8 score = 23, SD=5.6).

Discussion

Main findings

We assessed the feasibility and the potential health effects of a transmural collaborative care model for patients using APs treated in general practice. This pilot study shows that the intervention is executable in primary care, although it will not reach all eligible patients since many would not participate.

It appeared that 78% of participants were advised to change their use of AP now or in the future. Other advice concerned other medication, lifestyle, monitoring, and psychotherapy. At 3 months, 41% of all advice had been adopted. Of 10 smokers, four had quit smoking (40%). We found a small but significant improvement in the absolute QRISK3 score between baseline and follow-up. This result must be interpreted with caution because of the small number of participants and the high drop-out rate (36%). Dropping out was never associated with a reduction in AP medications. On the one hand, the participants who were motivated enough to do the follow-up visit were more likely to lower their QRISK3 score. On

the other hand, 43% (n=12) of the participants had no room for improvement on their QRISK3 score because it was already low at baseline and the follow-up time of 3 months was short. Therefore, the significant change seems a promising results.

Strengths and limitations

The main strength of this study is the real-life execution of an innovative and complex intervention that combines the skills of different professionals and has the potential to improve patients' cardiovascular health in primary care. We learned a lot about the characteristics of our target group and pitfalls that should be avoided in the trial.

A principal limitation was the low number of participants. A lot of eligible patients were not invited without a known reason, which could have led to selection bias. This was an unexpected outcome caused by the high workload of the GPs, who were already challenged by the COVID pandemic. We will adjust the inviting routine in such a way that the burden on practices is reduced. Many eligible patients were difficult to reach or unwilling to participate. Former research shows that patients with SMI are a vulnerable group who experience social problems on many often intertwined levels[39,40]. This could make them more difficult to reach, involve, and maintain follow-up. A qualitative study on patient factors that influence access to primary care found that such people often experience unstable housing and do not have a fixed address or telephone number[41].

Comparison with existing literature

A scoping review into cancer screening also found that people with SMI participate less often[42]. Factors involved are psychiatric symptoms, fear, distrust in the health care system, and low priority. Facilitators to participate are support, good health care experiences, and making participation easy[43].

Of all people who agreed to participate, 36% dropped out before the follow-up visit after 3 months. The reasons for dropout were in accordance with the aforementioned vulnerability to social problems[39,40]. The role of the patient coach with lived experience, to introduce sources of support within the community, can be important during and after the TACTIC intervention.

Our aim was to include patients who are not being treated by a psychiatrist. During the inclusion of patients, we learned that a selection of who is being treated by a psychiatrist

based on the correspondence in the EMR is unreliable because letters from the psychiatrist are often missing. This is in line with an article by van Hasselt et al. in 2015, describing poor communication between Dutch psychiatrists and GPs[44]. Guidelines on communication and responsibilities would be helpful. The NICE guidelines, contrary to the Dutch guidelines, make explicit recommendations regarding referral to secondary care, referral back to primary care, and monitoring and treatment of CVR factors[9].

Risk-estimation tools such as QRISK3 are not really suited to quantify change in CVR after an intervention. After all, every risk-lowering intervention needs time to reduce atherosclerosis. However, in daily practice, GPs use these tools to explain to patients how much a strategy will help them lower their risk. American researchers developed an algorithm that resulted in a one-page handout showing the modifiable risk factors for patients with SMI and their clinicians[45]. Patients in practices who used this tool had a 4% relative risk reduction in total modifiable CVR after 12 months compared with patients in control practices[45]. We also compared the QRISK change in modifiable risk factors: the proportional risk. In a consensus meeting, we discussed the use of a relative or absolute measure as the primary outcome for the upcoming trial. The meeting concluded that GPs find a change in absolute risk more convincing because relative risk may obscure the magnitude of the effect on CVR.

The construction of the QRISK3 algorithm causes a skewed distribution. Every risk factor contributes to a higher risk, and fewer people have an accumulation of risk factors. Many people, even in this population, have a QRISK3 score so low that they cannot improve it. A threshold QRISK3 score in the inclusion criteria for the trial will improve efficacy. It will also limit the number of eligible patients for each GP. Presuming that the large group of uninvited patients in this pilot study was the result of a lack of time from the GPs, a tightening of the inclusion criteria for the trial will also benefit feasibility.

Where do we set the QRISK3 threshold? The UK NICE guideline classifies a risk of 10% morbidity and mortality as high[12]. A risk threshold of 10% would have excluded 2/3 of our participants, mainly the younger ones because age is a strong contributor to the algorithm. Excluding the young would be undesirable because the QRISK3 algorithm may underpredict risk in young people with psychosis[46]. Besides, the review of APs is equally important for young people. We reached a consensus on setting the threshold at ≥5% as an additional inclusion criterion for the trial. Hopefully, TACTIC will have a spin-off effect that other patients with APs can benefit from through awareness among physicians and improved collaboration.

Conclusion

In conclusion, this pilot study was essential in preparation for a trial to evaluate health improvement. With a few adjustments, the trial seems expedient and feasible. The room for improvement of treatment appears to be high, given the advice to change the use of AP in 78% of the cases, and it seems possible to decrease CVR in patients using APs in primary care with the TACTIC intervention.

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Supplements

Project description "PLEK voor EPA"

There are still significant gaps in the areas of health, relationships, participation, and personal recovery among people with severe mental illness. In the Arnhem region, since 2016, general practitioners and their nurses, psychiatrists, nurses from mental health institutions, experts with lived experience, and representatives of the municipality have been working together to improve collaboration around these patients. The collaboration was tested in two pilot projects called "PLEK voor EPA". Patients were discussed in a multidisciplinary consultation where they, often with their loved ones or supervisors, were actively involved.

In one pilot project, the use of antipsychotics was a central topic, where the pros and cons were carefully considered. Every patient received personalized advice.

In the other pilot project, the focus was on discussing the wishes and opportunities for recovery care in the neighborhood. The goal was to enhance the quality of life through personal recovery.

Both pilot projects demonstrated how somatic and psychosocial care can be improved together for these individuals. The results were a description of the process, that can serve as an inspiration for others to follow.

Figure S. Flow-chart multidisciplinary meeting

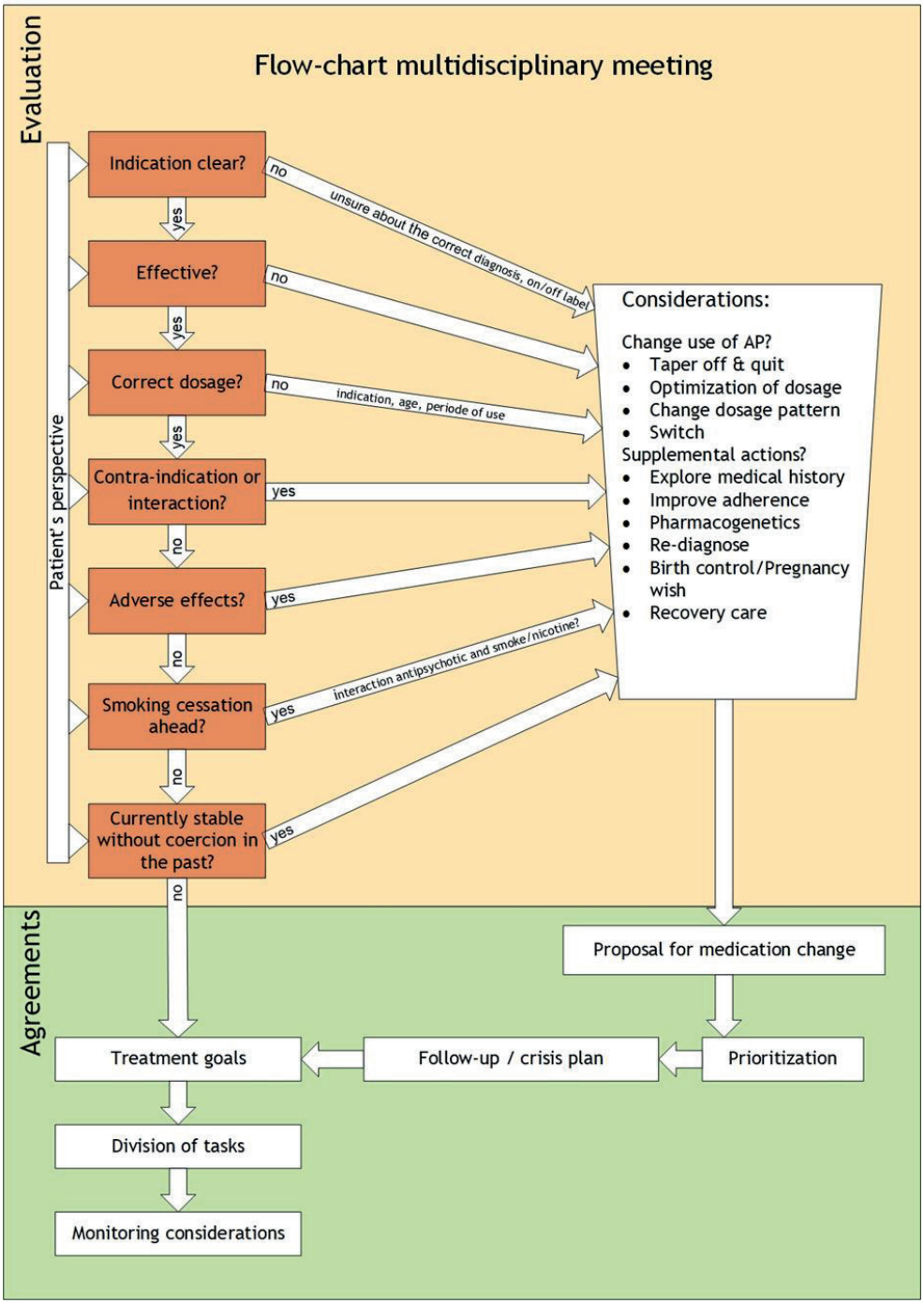


Table S1. Adjustments necessary to calculate a change in QRISK3 score.

Risk factor	Value at follow-up
Family history of premature coronary heart disease in a first-degree relative*	If yes, value at baseline is leveled to follow-up value
Antihypertensive medication**	If no, value at baseline is used as follow-up value
Age	Leveled to baseline

*This factor might not be known at the start of enrolment but does contribute to the patient's cardiovascular risk.

**If 'on blood pressure treatment' is answered 'yes', this will raise the QRISK3 score according to the algorithm. In case a patient starts blood pressure treatment due to the intervention, this will be ignored at follow-up.

Table S2. Overview of advice given during the multidisciplinary meetings.

Topic advice	Advice type	Advice given n (%)	Advice adopted n (%)
Medication	Stop AP medication	3 (11)	2 (67)
Medication	Reduce AP dosage	11 (41)	6 (55)
Medication	Switch risperidon to aripiprazol	1 (4)	1 (100)
Medication	Maintain AP dosage	5 (19)	5 (100)
Medication	Consider switch from risperidone to quetiapine to reduce dosage	1 (4)	0
Medication	Consider switch from quetiapine to amitryptiline for neuropatic pain/sleeping disorder	1 (4)	0
Medication	Consider switch from olanzapine to haldol or risperidone	1 (4)	0
Medication	Future/conditional advice: take AP only when needed	1 (4)	0
Medication	Future/conditional advice: consider reducing AP dosage	4 (15)	0
Medication	Future/conditional advice: stop AP	2 (7)	1 (50)
Medication	Future/conditional advice: consider switching AP agent	1 (4)	0
Medication	Start antidepressant medication	2 (7)	1 (50)
Medication	Reduce antidepressant dosage	7 (26)	1 (14)
Medication	Reduce benzodiazepine dosage	1 (4)	1 (100)
Medication	Do not take benzodiazepine every day	1 (4)	0
Medication	Future/conditional advice: reduce benzodiazepine dosage	1 (4)	0
Medication	Consider to stop opïoid medication	1 (4)	0
Medication	Future/conditional advice: start topiramate	3 (11)	1 (33)
Medication	Future/conditional advice: stop alfablocking medicine if continuation of topiramate	1 (4)	0
Medication	Reduce depakine dosage	1 (4)	0
Medication	Consider reducing dosage pregabaline	1 (4)	0
Medication	Change time of administration	2 (7)	?
Lifestyle	Quit smoking	5 (19)	4 (80)
Lifestyle	Future/conditional advice: quit smoking	1 (4)	0
Lifestyle	Lose weight	1 (4)	1 (100)
Lifestyle	Improve physical condition	2 (7)	2 (100)
Monitoring	Monitor how you feel every week on scale 1-10	1 (4)	?
Monitoring	Monitor adverse effects on muscles	1 (4)	1 (100)
Monitoring	Measure prolactine level in blood	1 (4)	?
Monitoring	Measure depakine level in blood	1 (4)	1 (100)
Monitoring	Involve family or carer if change is considered	4 (15)	0
Other treatment	Consider EMDR	1 (4)	0
Other treatment	Sleeptherapy	2 (7)	0

AP, antipsychotic; EMDR, eye movement desensitization and reprocessing.

Table S3. Changes in all secondary outcome variables of patients who completed follow-up (n = 18 unless mentioned otherwise).

QRISK3 variable	**T0 (SD)**	**T1 (SD)**	**T0–T1 (SD)**
Mean QRISK3 score	10.29 (12.55)	8.96 (11.10)	1.32 (2.84)
Mean QRISK3 score with TDS	10.99 (12.78)	9.47 (11.13)	1.52 (3.42)
Mean cholesterol ratio	4.05 (1.32)	4.10 (1.39)	–0.05 (0.40)
Mean systolic blood pressure	127.00 (19.43)	121.33 (14.58)	5.67 (9.34)
Mean SD of at least two most recent systolic blood pressure readings	6.83 (6.48)	6.27 (6.35)	–2.22 (4.52)
Mean BMI	26.98 (4.84)	26.83 (4.36)	0.14 (1.21)
Albumin creatinine ratio	0.82 (3.28)	0.31 (0.75)	0.64 (3.36)
Antihypertensive treatment	1	2	1
APs	18	15	3
Chronic corticosteroids	1	1	0
Chronic kidney disease stage 3–5	2	0	2
Mental health variable (n=21)	**T0**	**T1**	**T0–T1**
MHI-5 scores (SD)	59.52 (17.31)	61.43 (18.98)	–1.90 (15.04)
Smoking* (n=22)	**T0**	**T1**	**T0–T1**
Never	7	7	0
Past	8	12	–4
Light	4	3	1
Medium	3	0	3
Heavy	0	0	0
Adverse effects (n=21)	**T0**	**T1**	**T0–T1**
Mean adverse effects (SD)	22.57 (11.65)	17.33 (10.30)	5.24 (5.04)
EQ-5D (n=21)	**T0**	**T1**	**T0–T1**
Mean EQ-5D	0.33 (0.29)	0.42 (0.28)	–0.09 (0.24)

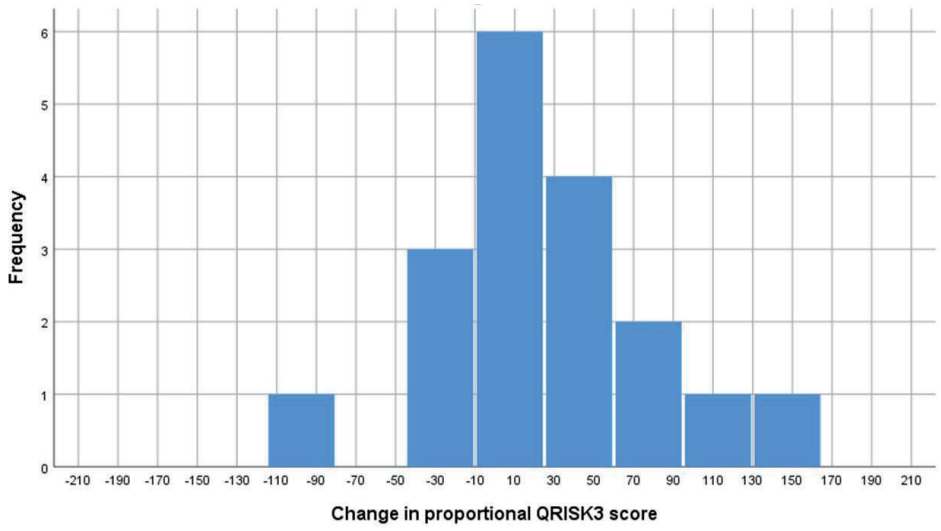
* Data derived from EMR and questionnaires.

AP, antipsychotic; BMI, body mass index; EQ-5D, generic quality of life; MHI, Mental Health Inventory; SD, standard deviation; TDS, Townsend deprivation score.

Additional analyses on QRISK3

The distribution of the proportional reduction in QRISK3 score, being the difference in QRISK3 score resulting from the intervention as a proportion of what could be achieved (a QRISK3 score with all modifiable risk factors optimized), is shown in Figure S2. For the 18 participants who had a complete follow-up, the risk reduction is presented on the x-axis. The mean improvement was 25.4% (SD=58.7). The proportional changes of three participants are outliers exceeding (–)100%. These participants had a very low maximum achievable improvement. A slight change in cholesterol ratio the wrong way (within the optimum range) or an improvement of systolic blood pressure (lower than what was defined as optimal) caused these outliers.

Figure S2. Distribution of proportional QRISK3 reduction.



Chapter 6

Cardiovascular risk management in patients using antipsychotics – a qualitative feasibility study

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Abstract

Background: Patients on antipsychotic medication have an increased risk of cardiovascular disease. In general practice, however, there is a lack of solid cardiovascular risk management for this specific group. TACTIC, a person-centered multidisciplinary cardiovascular risk program aimed to decrease cardiovascular risk and review antipsychotic medication use, was piloted in general practice.

Aim: To explore barriers and facilitators for delivering the TACTIC intervention, and assess which adjustments have to be made to evaluate its effectiveness and implementability in a future RCT.

Design and setting: Qualitative analysis of the feasibility study in three Dutch general practices.

Methods: We performed 8 individual interviews with patients and 2 focus group interviews with 11 healthcare professionals involved in the study. Interviews were semi-structured and topic guides were informed by the Normalization Process Theory. We used the Framework Method for the analysis of our data.

Results: Barriers were associated with experienced tension by patients due to participation, the course of the multidisciplinary meeting, and the high workload experienced by general practitioners. Facilitators were associated with the person-centered approach, the clear information meeting, and the ability to adjust roles in the intervention. Valuable suggestions for improvement were introducing a summary report from the psychiatrist, improving expectation management for patients and adjusting the definition of the target group.

Conclusion: Several adjustments to the TACTIC intervention are necessary before evaluation in a larger randomized controlled trial can take place. This work underlines the importance of performing a feasibility study prior to a trial to improve its effectiveness and efficacy.

How this fits in

Cardiovascular risk management, although common in general practice, is insufficiently applied to patients on antipsychotic medication, despite the knowledge that this patient group is at increased risk of developing cardiovascular disease. We developed TACTIC, a person-centered multidisciplinary intervention aimed at decreasing cardiovascular risk and reviewing medication use, and implemented it in three general practices. With this feasibility study, we

assessed the experiences of patients and healthcare professionals and explored the barriers and facilitators for delivering the TACTIC intervention, together with suggestions for improvement. The findings highlight the valuation of a person-centered approach in relatively vulnerable patients and underscore the importance of good expectation management and defining the appropriate target group for the intervention to succeed.

Introduction

Antipsychotic medication is used in general practice for the treatment of a range of disorders. Primarily, they are indicated for severe mental illnesses (SMIs), including schizophrenia, bipolar disorders, and affective psychoses, and are found effective[1-3]. Antipsychotic medication is prescribed to 1-2% of the general population[4,5]. A large proportion of antipsychotics, however, ranging from 35 to 77%, is prescribed off-label, for treatment of anxiety, dementia, and sleep- and personality disorders[4,6-11]. The use of atypical (or second-generation) antipsychotic medication (APM) is increasing worldwide[6,12-16], especially as a consequence of increased off-label use[6,17-20].

This raises concerns about the risk of severe side effects[6]. Use of APM is associated with an increased risk of cardiovascular events of 29% in women and 15% in men[21]. This is due to metabolic effects, such as glucose intolerance, dyslipidaemia, weight gain[22], and hypertension[23].

Even though the evidence of the increased cardiovascular risk (CVR) is well established, monitoring of patients is insufficient[24-29]. The clinical guideline for CVR management of the Dutch College of General Practitioners (NHG) does not even mention the use of APM as a risk factor[30]. In September 2024, an update of the guideline was published, only advising general practitioners (GPs) to consider drawing up a risk profile for patients with an SMI[31].

GPs are generally less aware of the side effects of APM than psychiatrists[32], which contributes to a lack of solid follow-up[33]. Unfortunately, GPs and psychiatrists often do not collaborate, even when it comes to reducing CVR in patients using APM[33]. Care involving collaboration and coordination between different levels of care, such as primary and secondary care, may have added value in reducing CVR in patients taking APM. In The Netherlands, this type of care is called “transmural” collaborative care.

Together with a multidisciplinary task force, consisting of relevant stakeholders in the eastern Netherlands[34], we developed a person-centered intervention to address these problems. Our intervention, called TACTIC, covers Transmural collaborative care regarding cardiovascular risk management and medication review for patients using AntipsyChoTICs[35]. With this intervention, GPs closely collaborate with patients, psychiatrists, and other disciplines to reduce CVR and review APM use. Based on advice with psychiatrist's input future steps are planned in a shared decision making process by GP and patient. TACTIC is considered a complex intervention, as defined by the British Medical Research Council, both due to the structure of the intervention, as well as the complexity that arises from the interaction between the intervention and the context in which it is implemented[36].

Aim

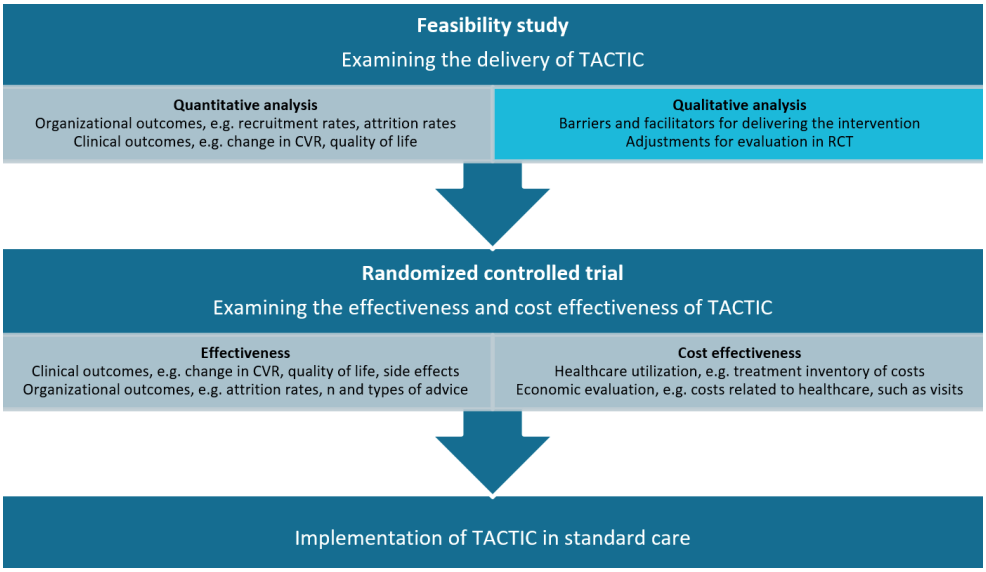
The purpose of this qualitative feasibility study was to assess the acceptability of the procedures of TACTIC and to explore barriers and facilitators for delivering the intervention. The results will provide suggestions for improvement in order to evaluate TACTICs effectiveness and implementability in a future randomized controlled trial.

Methods

Study design

This qualitative study is part of a larger TACTIC project, see Figure 1. As TACTIC is considered a complex intervention, it is recommended to perform a mixed methods feasibility study before conducting a trial[36]. In line with other studies, we use the term feasibility study as an overarching term for studies that aim to support the development of future studies[37,38]. Methods and results of the qualitative part of the feasibility study are presented in the current article. More detailed information on the quantitative part is published elsewhere[35].

Figure 1. Overview of the TACTIC project, with the current qualitative part of the feasibility study highlighted in light blue



CVR=cardiovascular risk

Setting and participants

The feasibility study took place in 2021. We implemented TACTIC in three general practices in an urbanized region in the eastern Netherlands at the same time and followed patients for three months.

TACTIC is aimed at patients using APM for at least three months, prescribed by their GP, who have no psychiatrist involved in their current treatment phase. Patients were excluded from participation when they were aged <25 or >84 years, had a diagnosis of dementia or organic psychosis, or had a history of cardiovascular disease (CVD).

GPs generated a list of eligible patients from the electronic medical records, based on mentioned in- and exclusion criteria, and subsequently invited the selected patients by telephone. Ultimately, 28 patients participated. The intervention was completed by 23, of whom 18 had a complete follow-up. At baseline dropouts did not differ from the participants who completed follow-up. Details on selection and patient flow have been described before[35].

Intervention

TACTIC consists of three consecutive steps: an information meeting, an MDM, and a shared decision-making (SDM) visit with the GP (Box 1). Patients are welcome and encouraged to bring a carer throughout the intervention to provide social support, as this can be a significant motivating factor[39,40].

Box 1. TACTIC intervention

Step 1	Information meeting
	The general practitioner invites all participating patients for an online information meeting in which information is given about the next step, a multidisciplinary meeting. Patients' carers (e.g. partners, relatives) are welcome to join the information meeting as well. The information meeting aims to motivate and prepare patients and their carers to participate in the multidisciplinary meeting. During and after the information meeting, several chatrooms are available in which patients are able to chat with either a healthcare professional (HCP), a researcher or the entire group of participants
Step 2	Multidisciplinary meeting
	A 15-minute MDM per patient is being held using a standardized format. In the meeting, the patient using antipsychotic medication (with or without their carer), the general practitioner, a psychiatrist, an person with lived experience, and the chronic care nurse will review the patient's antipsychotic use and all other medication (if applicable). Information on medication use has been provided in advance by the pharmacist. The meeting results in individualized treatment options including advice on antipsychotic use (continuation, deprescribing, or switching) and reducing cardiovascular risk. The options also define the tasks and responsibilities of the various HCPs
Step 3	Shared decision-making visit
	The patient (with their carer, if desired) visits the GP to translate the individualized treatment options into an action plan through shared-decision making. This shared-decision process benefits healthcare behavior change and adherence. Potential actions are, for example, deprescribing antipsychotics, initiating antihypertensive or cholesterol lowering drugs, smoking cessation, referral to the primary care mental health nurse, the chronic care nurse, the dietician, the physiotherapist, or to a lifestyle coach.

HCP=healthcare professional; MDM=multidisciplinary meeting; GP=general practitioner

Data collection

Four months after the implementation of TACTIC in the three general practices, we performed individual interviews with participating patients and their carers. Two focus group interviews were held with healthcare professionals (HCPs) involved in the feasibility study.

Due to the delicate subject of the study, we chose to interview patients individually, to ensure a safe environment in which they could speak openly about their personal experiences with TACTIC.

During the focus group meetings, however, we used the group dynamic and interaction among HCPs to help explore the barriers and facilitators in conducting TACTIC in-depth.

For the individual patient interviews, we purposively sampled patients who completed the entire intervention, based on CVR, gender, age, and on- or off-label use of APM, to make sure all relevant characteristics were represented. For the focus group interviews, we invited all HCPs involved in the study.

All participants received oral and written information about the study and its aims and were subsequently invited to participate.

KB conducted the individual interviews. The interviews took place at the patients' home, their working place, their general practice, online through video call, or by telephone, whichever was convenient for the patient. SG moderated the focus group interviews, and KB and KJ attended as observers. Due to the COVID-19 pandemic, we had to organize the focus groups digitally through video calls instead of in real life. We audio-recorded all interviews after obtaining informed consent. To protect the participants' identities, ID codes were used throughout data handling.

The individual and focus group interviews were semi-structured. The topic guides were informed by the four constructs of the Normalization Process Theory (NPT) (Supplementary Box 1)[41,42]. Questions focused on key trial parameters, addressing components such as sense-making, workability, enrolment, appraisal, and reconfiguration (Supplementary Tables 1 and 2). The guides were partly adapted to each participant category and initial findings influenced sequential topic guides to ensure we collected all necessary data to answer our research questions.

We applied the Standards for Reporting Qualitative Research (SRQR)[43].

Data analysis

We used the Framework Method for the analysis of our data (Supplementary Box 2)[44]. All interviews were transcribed verbatim and, after familiarization with the data, coded using Atlas.ti version 24.0.0. The first three individual interviews were coded by KB and KJ independently, after which they agreed on a set of codes to apply to all subsequent transcripts, which were then coded by KB. The focus group interviews were coded by KB and KJ independently, and after review with the research group they reached consensus.

We coded the data inductively using a thematic analysis. The NPT proved to be less helpful than anticipated and using NPT would ask for forcing the data into the predetermined constructs. For this reason we restricted the use of the NPT to the development of the interview guide and abandoned its use in the analyses. Consequently, codes were grouped into clearly defined categories by the research group, to form a working analytical framework. After applying the analytical framework to all transcripts, data were charted into a framework matrix and interpreted for analysis. Finally, during and after the pilot phase the project team discussed the lessons from the pilot to incorporate them in the effectiveness study.

Results

We conducted 8 individual interviews with patients and two focus group interviews with 11 out of 13 HCPs in total (two pharmacists canceled last minute, of whom one provided written input). During one individual interview, the patient's partner was also present. See Tables 1 and 2 for participant characteristics.

After six individual interviews, we presumed data saturation, after which two more interviews were performed to check and confirm data saturation.

Table 1. Participant characteristics individual interviews

Participant	Interview time (min.)	Risk of CVD (% QRISK3)	Gender (m/f)	Age (years)	AP-use (on-/off-label)
P02	50	10.6	m	54	On-label
P03	40	5.0	m	44	Off-label
P04	41	54.0	f	55	Off-label
P06 + C06	27	19.9	m	68	Off-label
P07	31	0.5	f	27	Off-label
P15	33	3.0	f	46	Off-label
P17	45	5.2	m	51	Off-label
P25	55	9.1	m	45	On-label

P=patient; C=carer; CVD=cardiovascular disease; QRISK3=10-year risk of cardiovascular disease; AP=antipsychotic medication

Table 2. Participant characteristics focus groups

Focus group session	Participant*	Occupation	General practice
1 **1h23min**	CN1	Chronic care nurse	1
	PE2	Person with lived experience	1
	GP1	General practitioner	1
	GP2	General practitioner	2
	GP3	General practitioner	3
	Ph1[†]	Pharmacist	1
	Ps	Psychiatrist	1, 2 and 3
2 **1h24min**	CN2	Chronic care nurse	2 and 3
	PE1	Person with lived experience	2 and 3
	GP4	General practitioner	1
	GP5	General practitioner	2
	Ph2	Pharmacist	1

CN=Chronic care nurse; PE=person with lived experience; GP=general practitioner; Ph=pharmacist; Ps=psychiatrist.

[†]Provided written input.

During familiarization and refining the framework, five main themes were identified. These were: goal of TACTIC, expectations of the intervention, experiences and feelings, communication and information, and the role of HCPs (Table 3).

Table 3. Themes and representative quotes related to TACTIC

Theme	Representative quote
Goal of TACTIC	"*What I do like is that there is structural attention to the possible negative side effects of medication*." P03
	"*Taking antipsychotics can pose health risks. By no means everyone knows this and for a long time it was not monitored either. So I'm glad that was done now, even with me as someone taking low-dose antipsychotics prescribed by my GP*." P25
	"*Before you go into the whole process, hey, if it's going to become a treatment method, estimate very carefully whether it really adds value for the patient in question.*" P03
	"*If indeed you already have people who [...] have low quetiapine use and are otherwise hardly at increased cardiovascular risk, you can cozy up to them and you can look at whether or not it's smart to continue using the drug, but when you say: how much health gain you're making, it's very limited*." Ps
	"*I mean: you don't aim for those people to stop taking pills, do you? You aim for those people to be stable and somewhat satisfied that they have all reasonable values, and you look at where you can make some adjustments, you adjust there. That's one, in my opinion. And you have those people who do have a poor risk profile, you want to adjust that. Those are your objectives, I think, briefly*." GP3
	"*Not, for example, revising the diagnosis or turning your whole medication policy upside down. Of course, suggestions can be made, but if that is too complex, it does not belong in general practice. Then you would have to refer that back to the psychiatrist again*." GP4
Expectations of the intervention	"*I, um, was dealing with some issues myself about medication and side effects. And um, yeah, so that actually came at a good time*" P02
	"*I basically had to explain my own situation and then we got some general tips back. So that was very disappointing for me. I get that they can't all look deep into*

	the file. I understand that too, but the idea behind it seemed very good to me. So that you talk to a number of people: are there other routes possible, other than just with your GP? But you really need more time for that and perhaps people need to have studied your file a little more, I think, if you really want such a group discussion to succeed." P17
	"*… maybe check at the beginning: this is what we want to talk about, what do you want to talk about? Otherwise there will be another one of those jack-in-the-box things at the end*" GP5
Experiences and feelings	"*I found it very stressful to participate. Because yes that ... It is drastic in your life when you are going to change something. I found that very stressful*." P06, "*He actually experienced it all very emotionally. From his own fear of: I can't do without antipsychotics*." C06
	"*A lot of people who use for a long time, they've been told: you have a lifelong condition or illness and you have to take medication for the rest of your life. And if you're going to phase that out then people might be afraid, because then there's going to be a crisis, and the care providers might also be afraid*." P25
	"*I think they might underestimate it a bit how exciting it is for participants. And certainly people who have been dependent on the drug for a long time. And that a bit more reassurance at the very beginning of that process is therefore necessary*." P06
	"*I very much felt that I had to defend my own point of view and stuff. And that the psychiatrist very much had the idea that I should want to taper or reduce and that the feeling came up very much like: that's the whole idea behind the study, that you just stop. Yes, ho, sorry, we're not going to do it like that.*" P07
	"That [GP] said: yes, we can also just watch it now and if later on you do feel the need to... to taper off or that you think it's necessary, yes, then we can still talk about it." P07
	"*I found it hard to stay motivated myself, to just keep participating throughout the study*." GP4
	"*When you talk about selection etc., it's about the goal you're aiming for. Are you aiming mainly to start seeing or working with patients who have an increased cardiovascular risk [...] then you could say: that is the category that is most relevant to look at critically*." Ps

Communication and information	"It made me feel like I was really participating in something. And that's different than just getting mail." P04
	"I did think it made sense that each discipline, each person involved briefly told who they were and what they were doing and what to expect. I think it was functional to know a little bit about who was involved." GP4
	"*What I can imagine is just some kind of standard video in terms of, say, the people participating in this project*." Ps
	"*And those cardiovascular diseases didn't actually come out er… clearly. And that… yes, if you look at it in retrospect, that could have been a bit clearer*." P02
	"*… people might have to read up on you just a little bit more, I think, for such a meeting to really succeed*." P17
	"I read them all, also as a piece of preparation when people came to me after three months. I did enjoy reading them. I also put them neatly in the medical record, absolutely great." CN1
The role of HCPs	"*It's the energy it took and the time it took and the yield, those were not feasible for me either*." GP5
	"*If the GP calls themselves, that does help, yes. That's pretty labour intensive, I do think, for the GP in this case, but it is the most effective way to include patients, I think*." GP1
	"*I think it does require a certain level of trust and you can't just let a random practice assistant make a call*." GP2
	"Multiple perspectives might help us forward. Yes, if that is done very openly, I think that is the right start." P17
	"Well, what I really liked about that is that there was room to indicate things. […] I had indicated: I don't want the expert with lived experience to be there. And that there was the possibility, that this was considered, of... yes, "that's possible! That can be arranged." P07
	"*There was not really an equal dialogue partnership. All of us could pay more attention to that, I think*." GP5
	"*Because then I also hear the stories from the patients and then I can build on that during the following consultation, or I think: 'oh yes, he can work with that, or that was the psychiatrist's suggestion'*." CN1

	"*The presence and input of the person with lived experience, for me it was a surprise how valuable and meaningful that was*." GP4
	"I think the person with lived experience, she wasn't – she didn't add anything for me, because she was coming from a completely different situation." P17
	" *The moment you would add experiential expertise of a good quality to the palette of your general practice, then it also falls much more into place.*" PE1
	"Yes, but yes, if I hadn't been there he wouldn't have... he would have dropped out." C01 *"I would have dropped out then, yes."* P06
	"At this stage of my rehabilitation, yes, I can largely provide myself with everything I need. In another phase, it might have been nice, if it were ten years back, or 15 years back." P25
	"*Now it was mostly a paper session, so you just look through the medication status and the tally sheet with the reported side effects, you link it together and you comment on that and you give the advice to taper off, but yes, if you don't know the patient or you have no additional information, then sometimes I know in advance that tapering off is really not possible and so it's useless advice.*" Ph2
	"*The advice of a pharmacist may contribute to good compliance and possibly also increase client involvement in treatment, and thus the success of the treatment.*" Ph1
	"If you think for instance: add another pharmacist, then it will only get busier and I don't think the patients would like that at all, because then there would be even more people they don't know. That's almost more threatening, I think." GP3

CN=Chronic care nurse; PE=person with lived experience; GP=general practitioner; Ph=pharmacist; Ps=psychiatrist.

Goal of TACTIC

Patients saw TACTIC as a relevant health check. They appreciated the attention to the metabolic effects of their treatment. Both patients and HCPs saw TACTIC as a suitable way to create more awareness and knowledge among GPs about the cardiovascular risk of APM, and it facilitated the start of regular monitoring.

In this feasibility study, all patients taking APM were approached by the GP. HCPs stated that a barrier due to approaching as many people as possible is, that you include the "worried well". Both patients and HCPs found it important to establish a well-defined

indication for TACTIC, where TACTIC should aim at patients who can really benefit from it. Since the goal of TACTIC is decreasing CVR, they suggested that TACTIC should target patients with a relatively high risk.

Both patients and HCPs suggested that it should be more clear that the goal of TACTIC is not tapering off or stopping APM per se, but adjusting where necessary and trying to reduce CVR where possible, taking into account the personal needs of the individual patient.

"Before you go into the whole process, hey, if it's going to become a treatment method, estimate very carefully whether it really adds value for the patient in question." P03

HCPs also stressed that the MDM should focus on the topic and should not be used to review a whole case or diagnosis.

Expectations of the intervention

Prior to the intervention, patients' expectations varied. Some merely wanted to discuss their side effects, and saw TACTIC as an excellent opportunity. Others expected to find more answers to their specific, personal questions. They felt a barrier in having to explain their problems and elaborate their questions to the HCPs.

HCPs noticed another barrier: their expectations did not always match those of the patients. Prior to the MDM, the objective of the meeting should be more clear. It was suggested that prior to the intervention, it should be specifically recorded what the patient wants to achieve. Sometimes it only became clear during the MDM what the patient's question was.

"… maybe check at the beginning: this is what we want to talk about, what do you want to talk about? Otherwise there will be another one of those jack-in-the-box things at the end" GP5

Experiences and feelings

Participating in TACTIC created tension in some patients. They were reluctant to change their medication, to let go of the certainty they experienced with their APM. They were afraid of relapsing or having a crisis. Because of this tension, they experienced a great amount of stress during the MDM, which was a barrier to active participation.

"I found it very stressful to participate. Because yes that ... It is drastic in your life when you are going to change something. I found that very stressful." P06, "He actually

experienced it all very emotionally. From his own fear of: I can't do without antipsychotics." C06

Several patients reported that their needs and ideas were addressed at the MDM. They experienced the MDM as pleasant. Others, however, perceived the setting of the MDM as a barrier as the amount of attendants was overwhelming and the MDM was mainly a conversation between the patient and the psychiatrist. Some patients experienced little openness to their choice of not wanting to change medication. They sometimes felt unheard.

The SDM visit was experienced as very pleasant by patients. Not all advice was immediately turned into action, but it was now open on the table, which facilitated consideration at a later date.

During the feasibility study, there was no limit in including patients, hence all patients taking APM were approached. This led to general practitioners experiencing a high workload, which felt as a great barrier for their engagement. HCPs expressed the opinion that the success of TACTIC depends on the level of CVR, but also on the patient's motivation. They considered TACTIC most useful for chronic APM users and patients with high CVR and suggest to specifically target these patients.

"When you talk about selection etc., it's about the goal you're aiming for. Are you aiming mainly to start seeing or working with patients who have an increased cardiovascular risk [...] then you could say: that is the category that is most relevant to look at critically." Ps

Communication and information

A facilitating factor in delivering the intervention was the information presented during the information meeting. Both HCPs and patients experienced it as a good preparation for the MDM. It facilitated in raising the right expectations and allowed the participating HCPs to introduce themselves. Patients regarded the information meeting as clear, but the information provided during invitation was, to some, already sufficient. From a pragmatic perspective, it was suggested that the webinar could be replaced by an information video.

"What I can imagine is just some kind of standard video in terms of, say, the people participating in this project." Ps

Information about CVD prevention was considered a facilitating factor by both patients and HCPs. This was also highlighted during TACTIC, but according to some patients, insufficient. While several patients reported that the attendants of the MDM were well informed, others expressed the opinion that the attending HCPs had not adequately reviewed their case prior to the MDM, particularly the psychiatrist. To them, this was perceived as a barrier during the MDM.

Without being asked, the psychiatrist wrote a detailed summary of his advice given during the MDM, to be used by the GP, the practice nurse, and the patient during the SDM visit and further follow-up. This was a well-appreciated facilitating factor by both patients and HCPs. With this summary, they had an overview of what had been discussed in the MDM. It gave them something to hold on to, something to read again because patients reported missing an evaluation with the psychiatrist during follow-up as a barrier to success.

> *"I read them all, also as a piece of preparation when people came to me after three months. I did enjoy reading them. I also put them neatly in the medical record, absolutely great." CN1*

The role of HCPs

The invitation of patients to TACTIC by the GP took a lot of time and effort and was perceived as an important barrier. However, GPs indicated that they consider personally calling and inviting patients, although very time-consuming, to be the most effective. The degree of trust established between a GP and the patient is a significant facilitator in this context, and it is not desirable to outsource this, according to the GPs, despite the high workload.

> *"It's the energy it took and the time it took and the yield, those were not feasible for me either." GP5*
>
> *"If the GP calls themselves, that does help, yes. That's pretty labour intensive, I do think, for the GP in this case, but it is the most effective way to include patients, I think." GP1*

The fact that TACTIC is multidisciplinary was being encouraged. Patients found it valuable that their individual situations were being looked at from different angles as this facilitated collaboration between different disciplines.

Patients were free to bring a carer and had the opportunity to determine whether the expert with lived experience would be present at the MDM. The ability to adjust the roles during the intervention was appreciated by the patients. It facilitated participation and gave them a sense of control.

It was found important by both patients and HCPs to attract the right professionals, tailored for the patient, where equality of roles within the MDM deserved attention.

According to some patients, the MDM could have been performed on a smaller scale, with only the patient, the GP, and the psychiatrist attending. The chronic care nurse, however, valued her participation in the MDM. This way, she had already met the patients, which facilitated monitoring them during follow-up.

The presence of the expert with lived experience was appreciated by both patients and HCPs. Because participation can be quite stressful, HCPs saw a facilitating role for the expert as a "sidekick" for the patient. The role of the expert, however, did not always fulfill its potential. A perceived barrier was the lack of clarity regarding the expert's role in the broader context of the intervention. The experts with lived experience mainly had value when they matched the patients in terms of problems.

Both patients and HCPs believed it was important to deploy an expert with adequate training and experience. The few patients who brought a carer appreciated their attendance. Furthermore, the carer saw a facilitating role for themselves. However, many patients saw no benefit in bringing a carer.

The added value of the medication review prior to the multidisciplinary meeting was questioned by both the pharmacist and the GPs. It was perceived as a barrier that the pharmacist executed the medication review on paper. Without a complete picture of the patient, they could only provide general advice. The pharmacist suggested to attend the MDM themselves, so that their input could be more useful. They felt that their advice may contribute to better treatment compliance when they speak directly with the patient. Consequently, increased patient's involvement may increase treatment success. However, GPs felt that a pharmacist would not belong in the MDM, also to prevent the MDM from becoming overcrowded. They suggested a personal review between GP and pharmacist prior to the MDM, to inform the GP with proper advice.

Discussion

Summary

This feasibility study revealed three main barriers to delivering TACTIC: the tension towards the intervention experienced by patients, the course of the multidisciplinary meeting, and the high workload for the GPs. The main facilitators were the person-centered approach, the clear information meeting, and the ability to adjust the roles during the course of the intervention, including bringing a carer. We identified valuable suggestions for improvement of the intervention amongst which are adjustments to the definition of the right target group, improving expectation management for patients, and introducing a summary report of the MDM from the psychiatrist. These findings are promising and show that, with some modifications, TACTIC is ready for evaluation in a large randomized controlled trial. In Table 4 we present an overview of the adaptations we made in the procedures of the upcoming trial.

Table 4. Adaptations to Trial Procedures

Problem	Solution
GPs spent too much time recruiting patients	Provide better support for GPs during recruitment
High workload at research sites	Maximize the number of patients per practice
Patients feared they would have to stop antipsychotics	Clearly state in patient information that discontinuation is not mandatory
Patients were insufficiently prepared for the MDM	Focus baseline consultation on patient goals; offer a consultation with a pharmacist or expert with lived experience
HCPs were insufficiently prepared for the MDM	Share patient expectations via the electronic medical record (EMR)
Missing data on prior antipsychotic use and mental health care	Add a patient questionnaire to capture medical history
Information meetings/webinars were not feasible for large-scale implementation	Replace webinars with videos featuring the patient's healthcare team
Need for a clear summary of advice	Request a report from the psychiatrist suitable for the GP, practice nurse, and patient

Strengths and limitations

This study provides valuable insights into the experiences and beliefs of patients and HCPs after the implementation of a new person-centered collaborative care intervention for patients on APM.

As far as we know, this is the first study to evaluate barriers and facilitators involved in delivering a transmural multidisciplinary intervention specifically aimed at lowering CVR in patients on APM, both with and without SMI, in general practice.

The topic guides were developed iteratively: each interview led to adjustments and was adapted to the situation. This led to increasingly richer data. After six patient interviews, data saturation appeared to have occurred, which was confirmed after conducting two additional interviews. This suggests that there was enough information gained to soundly answer our research questions.

To select patients for this qualitative study, we purposively sampled them. However, we only selected patients who completed the entire study and we were only able to interview those who we were able to reach and who were willing to participate. Perhaps patients who were not available for interviewing would provide other information than the patients we did interview. We have tried to facilitate participation in the interviews as much as possible by giving patients the choice of how, where, and when the interviews took place. Furthermore, since the vast majority of reasons for not completing the entire study were unrelated to the intervention, as reported by Jakobs et al.[35], the probability of highly divergent answers is low. Some selection bias, however, cannot be completely ruled out.

Due to COVID-19 measures, the focus group interviews could not take place physically. We were forced to hold them via video calling. Thanks to good instructions (e.g., everyone left their camera and microphone on, so that there was no obstacle to saying something), we tried to imitate a real group setting as much as possible. However, responding to non-verbal communication, such as gestures or facial expressions, is more difficult via video calling than in real life[45]. The advantage of focus groups via video calling was that all participants were recorded both as a group and individually, so that no information was lost when, for example, participants talked over each other.

As explained in the methods section, we chose to organize and present our findings according to the emerging themes, instead of using the NPT constructs, with the limitation that we did not use a theoretical framework in the analysis. We did use the NPT to inform our research

questions and topic guides. However, themes appeared too comprehensive to fit them into the predetermined constructs of the NPT, so we chose to present them in the same way as we analyzed them. This enabled us to use all valuable data derived from the interviews.

Comparison with existing literature

In our study, GPs experienced a high workload, which was partly attributable to patients being difficult to reach or failing to attend scheduled appointments. Literature shows that patients with an SMI have difficulty attending appointments[46], due to various reasons, associated with poverty, unstable housing, or side effects of mediation[40]. Other barriers can be motivation and adherence to treatment. It is crucial to consider these elements, as they are the very factors that can render CVD risk-lowering strategies more challenging in this target group[39]. Deployment of experts with lived experience could help to involve patients more, but also involving supportive others is a possible strategy to make CVR management more successful[39]. These experts with lived experience and carers can help manage appointments or even accompany patients to appointments[40]. In our study, relatively few carers were involved, and their value was viewed variably.

Patients mentioned that they were reluctant to change their medication. They were afraid of relapsing or having a crisis. This perceived tension had an impact on their participation in TACTIC. Crawford et al. also encountered this high level of concern, even leading to a low level of recruitment for their trial[47]. Patients who feel secure with their medication and/or experience fewer side effects may be more reluctant to change[47,48]. Since switching antipsychotic medication may increase the risk of relapse[49] or cause new side effects[50], patients' concerns are not unfounded. However, during TACTIC, medication is only changed on the advice of an experienced psychiatrist, when this is a safe option only, and always through shared decision-making. Patients must receive this reassurance in advance clearly, in order to facilitate participation in TACTIC.

This underscores the importance of proper expectation management, but also of the person-centered approach in TACTIC. Seen as a promoting factor for the intervention, personal and continuous care[51,52] is important for enrolling and retaining patients from a more or less vulnerable target group, as are patients in TACTIC.

As mentioned during the interviews, regarding the target group, it is important to establish a proper indication for TACTIC, meaning that TACTIC should not just focus on *every*

patient on APM, but merely on those with a *relevant risk* of developing CVD. There are various risk calculations for CVR in patients. In the Netherlands, SCORE2 is widely used in general practice[31], while in England QRISK3 is used[21]. In contrast with SCORE2, QRISK3 also includes the use of APM and having an SMI in the 10-year risk calculation[21]. Given the population of our interest, QRISK3 seems more appropriate to use in TACTIC. Introducing a threshold of a 5% 10-year risk for inclusion seems reasonable to the authors, as it would decrease the workload for GPs and hence benefit the feasibility of TACTIC[35]. Especially in young people with psychosis, the risk of developing CVD may be underpredicted with QRISK3[53]. Inviting these relative young patients with a relative low CVR will start a relation enabling follow up and early detection when risk factors like overweight do become apparent. Therefore, choosing a higher threshold of 10%, as is used in the UK NICE guideline on Cardiovascular Disease Risk Assessment and Reduction[54], would have the undesirable effect of excluding a large group of mainly young patients, for they generally do not reach 10%[35].

Implications for research and practice

This study yielded valuable lessons for redesigning and improving the TACTIC intervention. We combined both focus group and individual interviews, addressing the strengths of both methods and were able to conduct sufficient individual interviews in a hard-to-reach target group by adapting to their circumstances.

Intending to eventually implement TACTIC in standard practice, it is important to reduce the workload in deploying the intervention and increase its yield. The study findings do not only inform us in adjusting the intervention for further evaluation, they are also useful for other researchers developing complex interventions, especially in hard-to-reach target groups. The results highlight the valuation of a personal and person-centered approach in relatively vulnerable patients, and the ability to adjust roles, tailored to the patient. Our results underscore the importance of good expectation management as tension during an intervention may influence effectiveness. Defining the appropriate target group for an intervention will also improve efficacy.

All things considered, the analysis emphasizes the importance of performing a qualitative analysis as part of a mixed methods feasibility study prior to a larger trial when developing a complex intervention, as this approach is likely to enhance its effectiveness and efficacy.

With the right adjustments, TACTIC is ready to be evaluated in a large randomized controlled trial, with which the effectiveness and implementability can be further investigated.

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Ethical approval

Ethical approval was sought from the Medical Research Ethics Committee of the Radboud University Medical Centre (CMO file number 2020-7240). The committee concluded that this feasibility study did not fall within the remit of the Dutch Medical Research Involving Human Subjects Act (WMO).

Competing interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary

Supplementary Box 1. Normalization Process Theory

The four constructs of the Normalization Process Theory *Coherence* reflects the process of sense-making: do the users of the intervention understand its purpose? Can participants distinguish it from other interventions? *Cognitive participation* is about commitment: do HCPs agree that the intervention should be part of their work? Are the users willing to invest the time and energy necessary to support the intervention? *Collective action* contains the actual work of adopting the intervention: what changes should be made to perform the intervention adequately? How do these changes affect different roles? *Reflexive monitoring* is about appraisal: do participants assess the intervention as worthwhile? How effective and useful is it? Are there any changes needed in order to integrate the intervention in daily practice and make it sustainable?

Supplementary Table S1. Topic guide individual patient interviews

Main topics	**Subtopics**
General	
How did you experience participating in TACTIC? Please indicate whether it met your expectations.	• Is TACTIC different from the manner in which you have previously discussed your medication? • Prior to the intervention, did you understand its purpose? • To what extent did you consider the topic to be relevant to your own situation? • What is your perception of the duration of the intervention?
How do you value the format of TACTIC (preparatory visit with the general practitioner, information meeting as webinar, the multidisciplinary meeting, and the shared decision-making visit with the general practitioner)?	

Invitation	
You were invited to participate in this intervention by your general practitioner. Please indicate your preferred method of approaching you for participation.	• From whom would you prefer to receive information about the intervention?
Information meeting	
How did you experience the information meeting (the webinar, in which the multidisciplinary meeting was outlined in detail)?	• What were the aspects you found most appealing? • Please also describe the aspects you found least appealing. What aspects could be improved? • What was your assessment of the additional value of the information meeting, i.e.: was the information meeting necessary, or could it have been omitted without negatively impacting the intervention? • Did it help to remove tension/uncertainty regarding the multidisciplinary meeting?
Multidisciplinary meeting	
How did you experience the multidisciplinary meeting, in which you were given advice about your medication and your cardiovascular risk?	• How did the meeting go for you? • The objective was to obtain information and advice on the use of your medication and your risk of cardiovascular disease. In your opinion, did that occur? • What were the aspects you found most appealing? • Please also describe the aspects you found least appealing. What aspects could be improved? • Who do you think should attend the multidisciplinary meeting? • The pharmacist was now offering advice remotely. Would it be advantageous for them to be present at the table? • *In the event that a carer was present*: how did you experience being at the meeting together?

	• *In the event that the patient did not bring a carer*: in retrospect, would you have preferred to bring a carer to the meeting?
Shared decision-making visit and follow-up	
How did you experience the shared decision-making visit and follow-up?	• Was it nice having a shared decision-making visit? • Was it useful? • What were the aspects you found most appealing? • Please also describe the aspects you found least appealing. What aspects could be improved? • To what extent were you able to contribute to the formulation of the treatment plan? • Do you have any suggestions for how the shared decision-making visit and follow-up could be conducted more effectively?
Wrap up	
• Is there any additional information you would like to share, or any further topics you would like to discuss?	
• If you could give one ultimate recommendation, what do you believe is the most crucial factor in optimizing the effectiveness of TACTIC?	

Supplementary Table S2. Topic guide focus group interviews

Main topics	Subtopics
General	
As a healthcare professional, how did you experience the TACTIC intervention, i.e. approaching patients, the preparatory visit, the information meeting, the medication review, the multidisciplinary meeting, the shared decision-making visit, and follow-up?	• Overall, how did you feel about carrying out the intervention? • To what extent was the purpose of TACTIC clear beforehand? • Was it clear what tasks you had to perform, and when? • Did you have sufficient time and staff to implement TACTIC within your organization? • To what extent were the outcomes of the intervention and your actions evident to you?
Invitation	
How did you experience approaching patients and conducting preparatory visits?	• What factors facilitated you carrying out these tasks? • What were the limiting factors? • Please provide any further insights you may have regarding approaching patients for the intervention and conducting the preparatory visits
Information meeting	
How did you experience the information meeting and the webinar about TACTIC?	• What aspects of the information meeting did you find most beneficial? • Could you provide feedback on the aspects that could be improved? • Is it feasible in routine practice to organise an information meeting for new patients on an annual basis, for example? • What suggestions do you have for improving the information meeting? • Please provide any further insights you may have regarding the information meeting
Medication review	
To the pharmacists	• How did you experience the process of conducting the medication review?

	• Did you have enough time to execute the review?
To the receivers of the medication review	• What was your impression of the medication review? • Was it conducted in the right form? • Was the contribution sufficient?
To the whole group	• What is your opinion on the right form of involving the (role of the) pharmacist in TACTIC? • What were the facilitating factors in conducting or using the medication review? • What were the limiting factors? • Is there any additional information you would like to provide regarding the medication review?
Multidisciplinary meeting	
How did you experience the multidisciplinary meetings? (Considering the following aspects: preparation, format, content, roles, composition, time, number of patients addressed per meeting)	• What were the facilitating factors that contributed to the successful completion of the multidisciplinary meeting? • What were the limiting factors? • What suggestions can be made to enhance the feasibility of the multidisciplinary meetings? • What suggestions can be made to enhance its efficacy and outcomes?
Detailed summary written by the psychiatrist	
To the psychiatrist	• To what extent was writing a detailed summary feasible? • How much effort was required to write the summary?
To the receivers of the summary	• To what extent was the summary used by the receivers?
Shared decision-making visit (general practitioners)	
How did you experience the shared decision-making visit?	• How did the shared decision-making visits go? • To what extent were they beneficial to the process? • Do you have suggestions for optimizing the efficacy of the visits? • Is there any additional information you would like to provide regarding the shared decision-making visits?

Follow-up (chronic care nurses)	
How did you experience the follow-up?	• How did the follow-up consultations go? • To what extent were they beneficial to the process? • Do you have suggestions for optimizing the efficacy of the consultations? • Is there any additional information you would like to provide regarding the follow-up consultations?
Implementation	
• Do you think we can implement TACTIC on a national scale in its current form? • To what extent might TACTIC be integrated into standard care on a national scale, given the implementation of the suggested improvements in this meeting, and will it be sustainable?	
Wrap up	
• What do you consider to be the most crucial factor in ensuring the feasibility of TACTIC? • What do you consider to be the most crucial factor in ensuring that TACTIC is as effective as possible?	

Supplementary Box S2. Seven main stages of the Framework Method

Stage 1	Transcription
Stage 2	Familiarisation with the interview
Stage 3	Coding
Stage 4	Developing a working analytical framework
Stage 5	Applying the analytical framework
Stage 6	Charting data into the framework matrix
Stage 7	Interpreting the data

Chapter 7

Transmural Collaborative Care Model for Cardiovascular Risk Management and Medication Review in Patients Using Antipsychotics in Primary Care (TACTIC): a study protocol of an incomplete stepped wedge cluster randomized trial

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Abstract

Background: It is well established that patients with severe mental illness and those treated with atypical antipsychotics (AAPs) are at an increased risk of cardiovascular disease. However, primary care currently lacks adequate monitoring of AAP usage, its effects, and the associated cardiovascular risk. We have developed TACTIC, a transmural collaborative care model for patients using AAPs prescribed by the general practitioner (GP) to address the issues of potential overtreatment with AAPs and undertreatment for cardiovascular risk. TACTIC comprises three steps: an informative video for patients, a multidisciplinary meeting, and a shared decision-making consultation with the GP.

Objectives: To evaluate TACTIC's effectiveness on cardiovascular risk and mental health and its cost-effectiveness.

Methods: We will conduct an incomplete stepped wedge cluster randomized trial in the Netherlands.

40 GP-nurse clusters are randomized into four waves. Each cluster recruits adult patients (25-85 years), without prior diagnoses of dementia, delirium, or cardiovascular disease, for whom the GP prescribes AAPs. Every five months, a new wave starts with TACTIC. Measurements are taken before the intervention starts and every 5 months until the study concludes. Primary outcomes are cardiovascular risk and mental health as measured with the QRISK3 score and MHI5, respectively. The economic evaluation consists of two cost-utility analyses, one on the data collected alongside the trial and one based on a model extrapolating the trial data to a 10-year horizon. We will also evaluate the process of delivering TACTIC.

Conclusion: This study will assess TACTIC's (cost)effectiveness and provide insights for successful delivery in general practice.

Clinical Trials Registration: clinicaltrials.gov NCT05647980

Introduction

Prescriptions of Antipsychotics (APs) are on the rise worldwide[1]. In the Netherlands, the number of users increased by 48% from 2003 to 2022[2]. APs are prescribed for psychiatric disorders, including schizophrenia, bipolar disorder, schizoaffective disorder, and major depressive disorder. These conditions are commonly referred to as severe mental illness (SMI). However, it is important to note that a considerable number of patients who are prescribed APs do not have an SMI diagnosis[3]. Jakobs et al. found that among patients in general practices who use antipsychotic medication, up to 68% did not have a registered diagnosis of an SMI[4]. These patients are likely using APs off-label. Reasons for off-label prescription can be anxiety, agitation in dementia, sleep disorder, or challenging behavior of patients with an intellectual disability[5,6].

The use of APs, particularly atypical antipsychotics (AAPs), is associated with potentially serious adverse effects, including fatal arrhythmias and metabolic disturbances[7,8]. These adverse metabolic effects can develop in time and some APs are more likely to cause metabolic changes than others[7,9]. It is a well-known fact that individuals who suffer from severe mental illness tend to have a life expectancy that is 10-20 years shorter than the average person[10]. This is primarily due to an increased risk of mortality from cardiovascular disease (CVD)[8,11] , which is caused by several factors. Patients with SMI have a higher incidence of lifestyle risk factors, such as poor diet, lack of exercise, stress, and smoking, which can contribute to the development of CVD[12,13]. Moreover, the adverse effects of AAPs are an independent cardiovascular risk (CVR) factor[7,14,15].

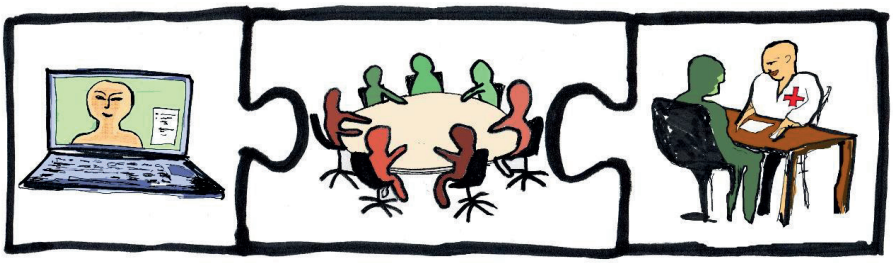
In the Netherlands, many patients on AAPs are discharged to primary care without a care plan for monitoring treatment effects, adherence, side effects, and management of CVR(4). The increased CVR in patients taking AAPs can be managed in general practices, with lifestyle counseling as well as pharmacological interventions, in the same way as managing CVR in other patient groups[16].

However, GPs are not as familiar with adjusting AAPs use as psychiatrists[17], GPs and psychiatrists often do not collaborate in reducing CVR in patients using AAPs[17], and patients with mental illness participate less often in preventive care programs[18]. The latter is explained by psychiatric symptoms, fear, distrust in the health care system, and low priority[19]. Furthermore, patients with mental illness are less likely to receive standard care because stigma toward these patients influences physicians' health decisions[20]. This may affect the

willingness to proactively invite patients with mental disorders using AAPs to monitor their CVR. As a result, when patients are referred to primary care in a stable phase, CVRM is lacking, and patients continue their AAP medication even if their risk has worsened over time.

To improve AAP monitoring and to reduce cardiovascular risk in patients using AAP in general practice, we have recently developed an intervention named" **T**ransmural collaborative care model for the review of **A**ntipsy**C**ho**TIC**s" (TACTIC, see further Fig.1 and the methods section).

Figure 1. The TACTIC intervention consists of an informative video for patients, a multidisciplinary meeting, and a shared decision visit.



To our knowledge, TACTIC is the first intervention focusing on medication review and primary prevention of cardiovascular disease in patients on AAPs in general practice. The TACTIC intervention aims to enhance healthcare services for a neglected population in Dutch primary care.

Study aims

The study aims to evaluate the impact of TACTIC on participants' health, assess the cost-utility of delivering TACTIC, and examine the process of delivery of TACTIC in the participating general practices.

Methods

Setting

This study will be conducted in general practices in the Netherlands.

Design

For the evaluation of TACTIC, we have chosen an incomplete stepped wedge cluster randomized trial (i-SWCRT), implemented from March 2023 until November 2024 (see Figure 2). The reason for not choosing a standard stepped wedge design, is the ensuing ethical problem of patients with an established high CVR who are withheld from treatment due to their GP's randomization in a standard stepped wedge design. For instance, if a patient is part of a cluster that belongs to wave four, according to a complete format, their first CVR screening will take place in March 2023 and will be repeated every five months until the intervention begins in June 2024. With an i-SWCRT, delivery of TACTIC, and initiation of CVR lowering strategies, would follow without delay in 6-8 weeks after the first CVR screening. Until the start of their wave, patients will continue to receive care as usual. Simulations to determine power showed that an i-SWCRT will provide sufficient power. This finding aligns with the general observation that i-SWCRTs offer nearly comparable power to complete SWCRTs[21].

We followed the SPIRIT guidance for reporting the content of this study protocol[22].

Eligibility

The criteria for patient inclusion and exclusion in the study are presented in Figure 2. The criteria are based on their ability to calculate the patient's QRISK3 score[15], which is used to assess their CVR (see further section 3.8.1 Primary outcomes). Patients with a history of cardiovascular disease, including acute myocardial infarction, acute coronary syndrome, heart failure, ischemic stroke, transient ischemic attack, peripheral artery disease, aortic aneurysm, or any revascularization procedure such as percutaneous coronary intervention or coronary artery bypass grafting are excluded due to the inability to calculate their QRISK3 score. We made a deliberate choice to exclude patients with a low QRISK3 score for the TACTIC intervention and set the cut-off value at 5% based on the findings of our pilot study[23]. We

considered that for the multidisciplinary meetings to be useful, the risk had to be high enough to justify their effort, as perceived by participants and care providers. This means that a higher risk level would lead to a more meaningful discussion. However, we also wanted to avoid excluding all young people. Our pilot study[23] found that setting the limit at 10% would result in such exclusion due to the strong correlation between the risk estimate and age. In the regular Dutch CVRM program, the CVR risk assessment is conducted using the SCORE calculation[16]. A QRISK3 score of 5% is not comparable to a SCORE of 5%, because the first indicates morbidity and mortality due to CVD and the latter only mortality. We chose QRISK3 above SCORE, because SCORE does not consider the additional risk associated with having an SMI or using an AAP and is not validated to assess the risk for patients with diabetes. For patients with diabetes, the dilemma regarding the use of AAP is even more urgent than for those without. For this study, we will use the QRISK3 score[10] to calculate the change in CVR specifically associated with SMI and AAP. We will invite patients with a QRISK3 ≥5% to participate in the i-SWCRT. If the QRISK3 score is below 5%, the patient does not meet the study criteria and will be cared for by their GP depending on regional agreements concerning CVRM.

Recruitment

Recruitment of general practices

We will recruit GPs through a video shared through social media platforms and with primary care co-operatives. Dutch GPs are well organized in regional primary care co-operatives, which aim to provide high-quality chronic disease management in primary care for patients with diabetes mellitus, cardiovascular diseases, high CVR, COPD, asthma, mental health needs, and frailty in old age[24-26].

Patient recruitment

An algorithm has been developed to identify eligible patients for this study[27]. The algorithm uses routine health data recorded by GPs in the electronic medical records (EMR). Participating GPs will use this algorithm on their EMR to generate a list of potentially eligible patients. The algorithm will consider patients who meet the study criteria and have an estimated QRISK3 score of at least 4%, based on the available data in their medical records.

As the algorithm could underestimate the CVR due to missing data, we chose 4% as a more conservative cut-off than the 5% that we use as the inclusion criterion. However, definite eligibility will be determined by a CVR screening in the practice. After the start of the cluster, all identified patients receive an invitational letter from their GP, informing them about the upcoming screening. Patients interested in participating are invited to contact the general practice. For patients who do not respond to the letter, the practice will call them by phone to invite them to assess their CVR. For the CVR assessment, all variables of QRISK3 are mapped using data from the EMR, supplemented with blood and urine tests, and questionnaires (See Table A2 in the Appendix for more information). The maximum number of patients per cluster is limited to 15, as the pilot study found this to be the maximum the cluster could effectively handle within the given timeframe.

Patient consent

Once the patient is deemed eligible, the investigator will contact the patient to confirm their willingness to participate in the study. We also provide a patient information letter, with an "easy reading" version for patients with low literacy. The patient, along with their guardian if applicable, will be asked to provide written informed consent. If desired, the patient can contact an independent physician knowledgeable about the study but not involved in its execution.

Randomization

A cluster refers to a (group of) GP(s) who work(s) with one nurse. If a large practice has two nurses for its CVRM program, then the practice will have two clusters. The GPs who collaborate with the same nurse are added to that nurse's cluster. We have decided to randomly assign the GP-nurse clusters to avoid bias due to practice characteristics and contamination caused by GPs and nurses becoming aware of the consequences of using AAP. This awareness can influence how they treat patients who are using AAP, which could in turn affect the baseline measurements. Contamination in a practice consisting of two clusters is limited because such cases are exceptional. The clusters will be randomized to either of the four waves, as shown in Fig. 2. The randomization process is stratified based on two factors. The first factor is the number of eligible patients on the list of each GP in the cluster (<19, 19-24, >24). The second factor is the population size of the city where the practice is located

(<300,000 or ≥300,000). The stratification of the city size will reduce the potentially diluting effect of metropolitan problems or regional interventions concerning CVRM. A minimization program is used to stratify with a random element and ensure balance in the allocation of the two factors over the waves. Blinding of the cluster as to their moment of implementing TACTIC was not possible. Due to the cross-over character, each participant will receive the intervention at some point in the study.

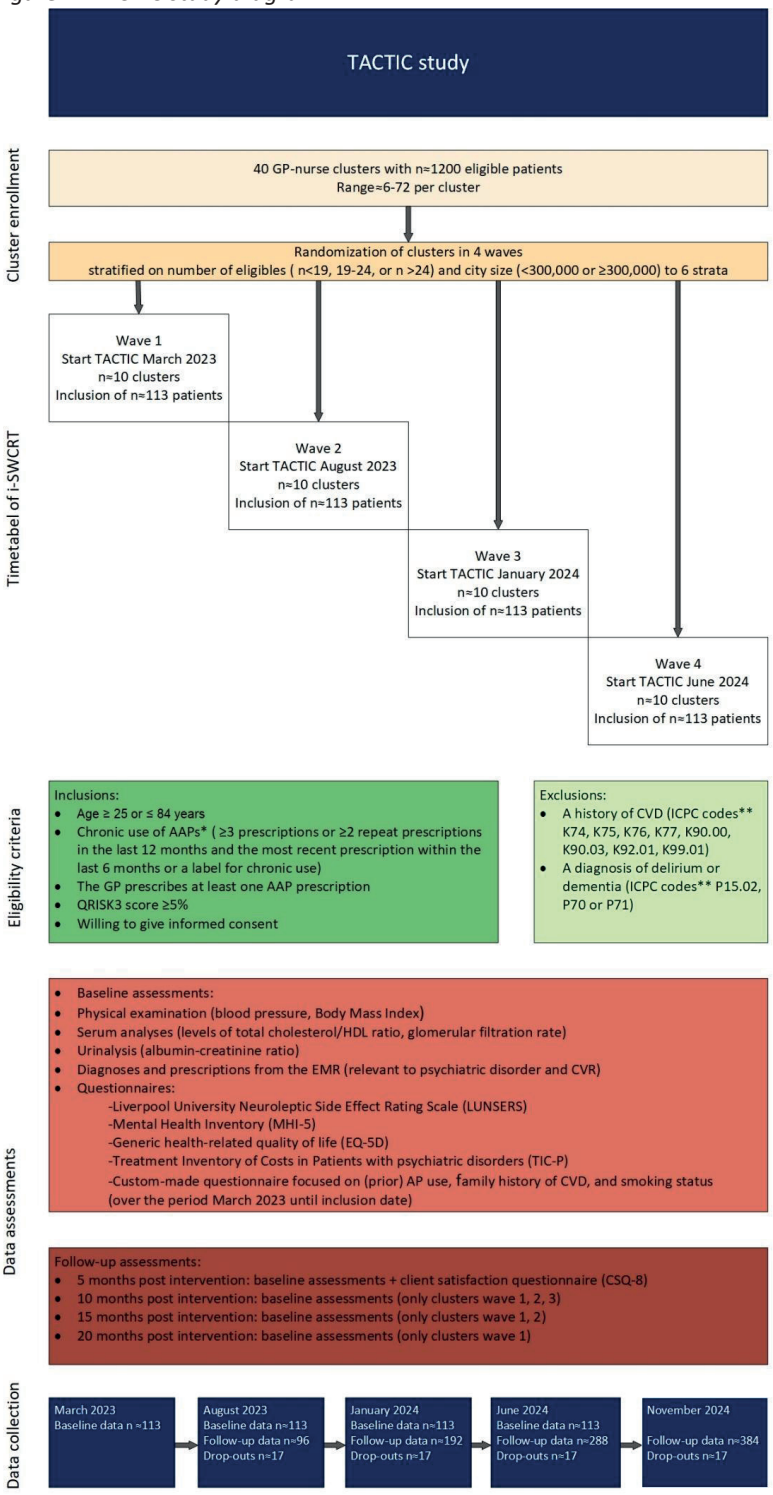
(Legenda to figure 2 on the next page)

*The prescriptions from the ATC codes(28). The ATC codes are similar to those in the QRISK3 algorithm as far as they are registered in the Netherlands: N05AX12, N05AD06, N05AH02, N05AE05, N05AH03, N05AX13, N05AH04, N05AX08, N05AE03, N05AX15, N05AX16

**The diagnoses from the ICPC codes(29).

Abbreviations: AAP, atypical antipsychotic; AP, antipsychotic; ATC, anatomical therapeutic chemical; CVD, cardiovascular disease; CVRM, cardiovascular risk management; CVD, cardiovascular disorder; EMR, electronic medical records; GP, general practitioner; HDL, high-density lipoprotein; ICPC, International Classification of Primary Care; i-SWCRT, incomplete stepped wedge cluster randomized trial; QRISK3, a tool to calculate the estimated CVD risk within the next 10 years for people aged between 25 and 84 without CVD.

Figure 2. TACTIC study diagram.



Intervention

TACTIC is a one-time intervention that takes place in the general practice setting (see Fig. 1). The design resulted from a project among healthcare professionals and patients in the region of Arnhem[30]. We have recently conducted a pilot study and found that the delivery of TACTIC in general practice was feasible[23].

TACTIC entails three consecutive steps in addition to usual care.

Step 1: All participating patients are shown an information video to inform them about the upcoming multidisciplinary meeting. The information video aims to motivate and prepare patients (and their carers) to participate in the multidisciplinary meeting. All healthcare professionals who take part in the multidisciplinary meeting will introduce themselves. The video will last 10 to 15 minutes and will be tailored for various multidisciplinary meeting settings.

Patients are encouraged to meet with their pharmacist or a person with a lived experience of an SMI to prepare for the multidisciplinary meeting, as was advised by participants in our pilot study.

Step 2: For every patient, a multidisciplinary meeting of 15 minutes will be conducted. The GP will send the relevant medical information to the psychiatrist at least one week before the meeting to allow for preparation. Most GPs open a so-called 'digital consultation' for the psychiatrist, which provides access to specific parts of the EMR of the GP. This includes the baseline assessments (see Figure 2), the results of any advice provided by the pharmacist (if applicable), and the most recent correspondence of secondary mental health care (if applicable). During the multidisciplinary meeting, the participating patient (and carer), the general practitioner, a psychiatrist, the primary care nurse, and a person with a lived experience of an SMI will discuss the patient's AAP use following a structure of topics, shown in Appendix Figure A1. Additionally, all elevated CVR factors will be addressed. The multidisciplinary meeting will provide a set of personalized treatment recommendations, including advice on AAP use (e.g., continuation, deprescribing, or switching) and reducing other CVR factors (e.g., lifestyle changes, hypertension treatment, cholesterol regulation).

Step 3: Following the multidisciplinary meeting, the patients will have a scheduled appointment with their GP within a week. During this visit, they will work together to devise a customized action plan based on the recommended treatment options. The plan will outline

the tasks and responsibilities of different healthcare providers. Potential actions are altering AAP use, initiating antihypertensive medication or statins, referral to the chronic care nurse for example for smoking cessation, referral to the primary care mental health nurse, the dietician, the physical therapist, or a lifestyle coach. After Step 3, the nurse will typically assess the effectiveness of the plan and monitor it in the future. If necessary, other healthcare providers may be consulted or involved

Participant compensation

All costs patients will make for the measurements in the laboratory will be reimbursed.

Outcome measures

Primary outcomes

We defined two primary outcomes, namely the change in CVR and the change in mental health status. For the CVR assessment, we use the QRISK3 score[15]. The QRISK3 is the preferred algorithm for assessing CVR according to the NICE guidelines for Cardiovascular Disease(31). The algorithm requires information such as ethnicity, the use of AAP, and relevant diagnoses such as SMI to calculate CVR (see Table S1 for QRISK3 variables). SMI includes schizophrenia, bipolar disorder, psychosis, and moderate/severe depression. However, in the Netherlands, the degree of severity cannot be deduced from the EMR. The CVR of patients with mild depression would be overestimated and therefore depression will not be classified as an SMI in our analysis.

QRISK3 is developed as a screening instrument. We will make the following adjustments to make the QRISK3 score algorithm usable to measure change. For age, we will use age at baseline (T0) at all measurement points. In the QRISK3 algorithm blood pressure treatment is considered a risk factor for CVR, as the patient on blood pressure treatment is considered a known case of hypertension. As a result, during the trial, the QRISK3 score may increase if the first prescription for blood pressure treatment is due to the intervention. To measure a change in QRISK3-score as correctly as possible, we will disregard the variable 'blood pressure treatment' in the algorithm during follow-up. If a participant reports a family history of cardiovascular disease (CVD) at any point during the trial, we will consider this information at all measurement points. This is because a positive family history of CVD is a

characteristic that is not dependent on time and influences the patient's cardiovascular risk (CVR) before the status of the family history is known.

Unfortunately, the Townsend deprivation score cannot be applied to the Dutch population. Therefore, it will be set to zero as instructed on the website https://qrisk.org[32], indicating neither deprivation nor affluence. The QRISK3 score can range from 0 to 100%. We consider a decrease of 2.5% points as clinically relevant (number needed to treat = 40).

For the mental health status, we use the five-item version of the Mental Health Inventory (MHI-5)[33]. The MHI-5 ranges from 0 to 100, where a score of 100 equals perfect mental health. In the absence of an established minimum clinically important difference (MCID), we followed Cohen's interpretation of a small effect defined as 0.2 x the SD. In our pilot study, 17 patients with a QRISK3 ≥5% had an SD of 15.2 for the MHI-5. Therefore, we will consider an increase of 3 points for an individual as clinically important[34]. See further Table A2. in the Appendix.

Secondary outcomes

Five secondary outcome measures will also be examined: change in the generic health-related quality of life, as measured with the EuroQol-5D-5L[35]; changes in side effects of antipsychotic medication, as measured with the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) questionnaire[36]; participants' satisfaction with TACTIC, as measured with the 8-item Client Satisfaction Questionnaire (CSQ-8)[37]; change in QRISK3 score with the Dutch deprivation score entered in the algorithm; and change in risk score as a proportion of the maximum achievable change in QRISK3 score.

Additionally, we will be measuring the delivery and uptake of TACTIC, including the number and content of advice given and the follow-up actions taken. Moreover, we will be examining healthcare utilization and productivity losses (TIC-P)[38], while also exploring how much TACTIC was used by the participating practices and identifying the factors that contribute to its successful delivery.

To provide a clear description of our measurements and questionnaires, we have included Table S1, which outlines the scores, ranges, and relevance of each.

Planned statistical analysis

All measured data will be assembled in a computer database and analyzed using SPSS 29.

Descriptive statistics

Descriptive analyses will be performed to describe the patient's characteristics at inclusion across the waves. Mean and standard deviation (SD) or median and interquartile range for continuous variables and numbers and percentages for categorical variables will be presented.

Analyses for primary outcomes

The effect of treatment on the outcome measures measured at 5, 10, 15, and 20 months of follow-up will be analyzed with mixed three-level linear or logistic regression, considering that the times of measurement are clustered within patients, and patients within general practices. Random effects for clusters and patients nested within a cluster are used to capture the correlation of patients within clusters and the correlation of measurements within patients. To test the effect of the intervention we will use a model with intervention “off” in the first measurement and “on” in the following measurements of a patient. A value of $p<0.05$ will indicate statistical significance for all analyses based on two-sided testing. The change in MHI-5 will only be tested if the first primary outcome, the change in QRISK3, is statistically significant.

Sample size calculation for primary outcomes

The sample size calculation for a power of 80% (see Appendix A3 for the formula) is based on the following findings and expectations. Our pilot study showed an SD of 12 for a single QRISK3 measurement, along with a mean reduction of 1.9 points in the QRISK3 score for patients who had a baseline QRISK3 score of ≥5% (unpublished results of our pilot study). This was after a 3-month follow-up period with suboptimal intervention conditions, including inadequate preparation of participating patients, leading to unclear expectation management. We expect that in the trial, after the optimization of the TACTIC procedures, we will be able to detect a reduction of a clinically relevant mean QRISK3 score of at least 2.5 points in the intervention group, compared to the control condition. 500 simulated trials indicate that 4 waves, 32 clusters with 12 patients each, are needed to provide a power of at least 80%, given an SD of 12, an intra-cluster correlation (ICC) of 0.10, a (test-retest) reliability on patient level of 0.95,

assuming a reliability on cluster level of 1, and an α of 0.05. We chose a drop-out rate of 15%. This is a considerate choice given the rates observed in our pilot study of 20% (based on a selection of participants with a QRISK3≥5%) and the drop-out rate of less than 10% in a UK primary care study evaluating a comparable intervention in a similar patient group[39]. In our trial, we have changed our approach from the pilot study. Now, participants are encouraged to meet with their pharmacist or a person with lived experience to prepare for the multidisciplinary meeting. This change in approach is aimed at reducing the number of dropouts compared to those in the pilot study. The required total number of remaining participants will be 384 patients.

Additional analyses

We will perform two additional analyses to support the primary analysis. In both additional analyses, we will use more data from the included patients in the current i-SWCRT.

1. We will use variables of QRISK3 found in the EMR of participating patients of waves 2, 3, and 4, which may be measured as routine care between the trial start date (01-March-2023) and the date of inclusion, and data on smoking status as collected in the questionary at baseline.

2. QRISK3 variables of the period between the trial start date and the date of inclusion that are missing in the EMR will be imputed.

Patients eligible at enrolment for their wave may be non-eligible at the start of the study. We will exclude these patients from these analyses.

Economic evaluation

The cost-utility of TACTIC compared to usual care will be performed alongside the clinical trial and will comprise a medical and societal perspective. Effectiveness will be expressed as Quality-adjusted life year (QALY) estimated according to the trapezium rule with utilities derived from the EQ5D5L questionnaire[35]. At the patient level, volumes of care related to the treatment of underlying diseases of this patient group costs related to performing TACTIC, medication costs, and productivity losses will be measured using data extraction from the

electronic medical patient files or otherwise by the TIC-P Questionnaire[38]. For further explanation see Appendix A4.

Research ethics

This study will be conducted according to the principles of the Declaration of Helsinki of 2013. Ethical approval for this study was waived by the local Medical Research Ethics Committee Arnhem/Nijmegen (file number 2022-15835)

Discussion

There is a lack of information regarding the effectiveness of CVR-reducing interventions in primary care patients who are taking antipsychotics. The TACTIC intervention is one of the first collaborative care interventions to address the issues of overtreatment with AAPs and undertreatment for cardiovascular risk in primary care. TACTIC offers personalized advice and involves patients in their meetings. The i-SWCRT design enables CVR-lowering strategies without delay for all participants. It ensures a high level of evidence while requiring fewer participants than in a classic randomized controlled trial. This complex intervention and its study design were carefully considered based on the results of our pilot study[23].

It is important to note that our study will possibly have limitations that should be considered. Firstly, GPs and psychiatrists must be able to safely share relevant patient information using a digital system that is available locally. However, it may be difficult to implement this approach in regions that do not have access to such a system. Secondly, it is expected that enrolling an appropriate number of patients in the study may be difficult due to the characteristics of this hard-to-reach group[18,19]. Our approach to enrolling patients in the study involves requesting their GP to invite them for CVR screening and then inviting them to participate in the study after explaining the screening results. To make the enrolment process easier, we will provide an additional version of the patient information that is easy to read. Additionally, we will emphasize to patients that they have complete freedom to decide whether they want to follow the advice given and address any concerns about changes in medication. We reduced the risk of selection bias as much as possible by recruiting GPs in multiple regions in the Netherlands and by randomizing the list of eligible patients before inclusion. Yet, there may be a risk of selection bias among both.

In conclusion, this study will assess TACTIC's (cost)effectiveness and provide insights for successful delivery in general practice. Collaboration during a multidisciplinary meeting can enhance awareness and promote the exchange of knowledge among general practitioners, psychiatrists, nurses, and individuals with a history of severe mental illness. This can ultimately improve the quality of care provided to other patients.

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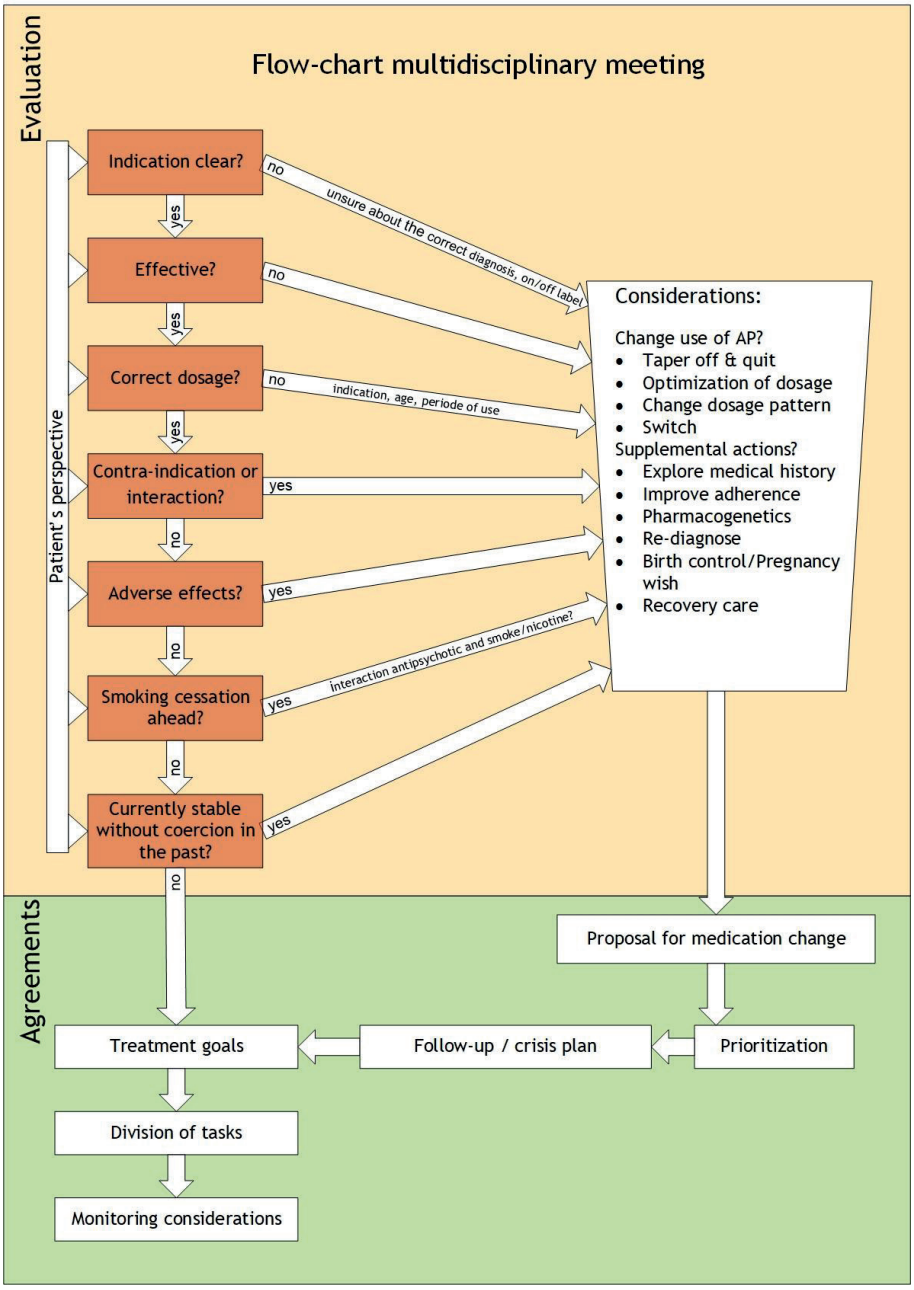
Appendix

Figure A1. The structure of the multidisciplinary meeting.



The flow-chart resulted from a project among healthcare professionals and patients in the region of Arnhem(30)

Table A2. TACTIC trial outcome measures and schedule of measurements

Topic	Construction	Description	Timeline*
Mental health	Primary psychiatric diagnosis	Diagnosis in the EMR.	0
	Mental health questionnaire	The Mental Health Inventory, a five-item version (MHI-5), is a measure of mental health(33). The MHI-5 is a derivative of the 36-item short-form health survey, the SF36, and assesses symptoms of depression and anxiety, loss of behavioral or emotional control, and psychological well-being in the prior four weeks. The MHI-5 ranges from 0 to 100, where a score of 100 equals perfect mental health. A score of 60 or higher is seen as good mental health, whereas a score below 60 is seen as poor mental health.	0, 5, 10, 15, 20
AP	AAP prescription	EMR concerning actual use, prescription in the past (until 5 years back), prescriber GP or psychiatrist, on- or off-label, change in daily dose, stop of AAP.	0, 5, 10, 15, 20
	Adverse effects AP questionnaire	The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) is a self-rating scale for measuring the side effects of AP medications(36). LUNSERS was developed by researchers within the University of Liverpool to indicate the extent of side effects experienced by patients medicated with neuroleptic drugs. The scale consists of 41 known side effects of neuroleptics. Each 'side-effect' listed is scored on a five-point rating scale of 0 – 4, i.e., 0 = 'Not at all' and 4 = Very much. A total score can be calculated by adding all item scores and then be graded into 'very low', 'low', 'average', 'high', and 'very high', based on the percentiles. A clinically relevant improvement of at least the minimal clinically important difference (MCID), is defined as 0.5 x SD of the baseline mean.	0, 5, 10, 15, 20
	Participants' perception of AAP pros and cons questionnaire	A custom-made questionnaire on AAP use with 10 questions which consists of 2 open questions about the reason for the use and the effectivity of the use, and 8 yes/no questions concerning health workers involved (psychiatrist, coach), pregnancy, safety (drug addiction, restraining measures, suicide attempt, relapse prevention plan, presence of (informal) caregiver in case of change in medication).	0
QRISK3	EMR, demographic	Age, gender, and financial records that are indicative of socioeconomic status.	0, 5, 10, 15, 20
	EMR, medication	Blood pressure treatment, steroid tablets, treatment for erectile dysfunction, or AAPs.	0, 5, 10, 15, 20

	EMR, diagnostic	Levels of total cholesterol/HDL ratio, glomerular filtration rate, albumin-creatinine ratio, systolic blood pressure, variability of blood pressure (standard deviation), and Body Mass Index.	0, 5, 10, 15, 20
	EMR, diseases, and disorders	Having a diagnosis of severe mental illness (this includes schizophrenia, bipolar disorder, and moderate/severe depression), diabetes mellitus, chronic kidney disease, atrial fibrillation, migraines, rheumatoid arthritis, systemic lupus erythematosus, or erectile dysfunction.	0, 5, 10, 15, 20
	EMR, diagnostic, and a risk factor questionnaire	Additional 7 questions concerning ethnicity, smoking status, a history of premature coronary heart disease in a first-degree relative, education, and marital state.	0, 5, 10, 15, 20
	Proportion of patients with a QRISK3 change of ≥2.5%	The proportion of patients who reach an absolute risk reduction of 2.5% at the end of follow-up, which we consider as a clinically relevant change.	5, 10, 15, 20
	Proportional risk reduction of QRISK3	The proportional risk reduction is defined as 'the change in QRISK3 score as a proportion of the maximum achievable change in QRISK3 score'. To give an example: a patient has a 10-year CVR of 20%, but after perfectly optimizing all changeable risk factors, can reach a 10-year cardiovascular risk of 10%. When, at the end of follow-up, the patient reaches a QRISK3 score of 17%, this means the patient reached a 3% absolute risk reduction (i.e., 20% - 17%), and a 30% proportional risk reduction (i.e., 3% / (20% - 10%)).	5, 10, 15, 20
	QRISK3 with a modified Townsend Deprivation Score	The Townsend Deprivation Score does not apply to the Dutch population. We want to perform a secondary analysis on the QRISK3 score in which we use the Dutch equivalent of deprivation. In the Netherlands, we use a deprivation index for patients with low socioeconomic status, based on employment, income, and percentage of non-western immigrants, "achterstandsindex"(40). This deprivation index applies to approximately 10% of the Dutch population. We decided to apply the Townsend Deprivation Score at p20 (below which are the 20% most deprived of the British population) for the 10% most deprived patients in our population. By choosing p20 instead of p10, we stay on the safe side and might underestimate the effect of deprivation, but we consider this more important than overestimating its impact.	

Quality of life	Quality of life questionnaire	Health-related quality of life will be measured with the EuroQol-5D-5L (EQ-5D)(35). This instrument is available in a validated Dutch translation. The EQ-5D comprises five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D index is obtained by applying predetermined weights to the five domains and ranges from 0 to 1, where a score of 1 equals perfect health.	0, 5, 10, 15, 20
Patient Satisfaction	Satisfaction with care questionnaire	The 8-item Client Satisfaction Questionnaire (CSQ-8) to measure participants' satisfaction with care(37) has a 4-point Likert scale. The sum of 8 sub-scores about different aspects of received care can vary between 8 and 32. Higher scores mean higher satisfaction. This questionnaire is recommended for use in psychiatric patients and has a Dutch-validated version(41).	5
Delivery of TACTIC	EMR. Records concerning plans	Number and percentage of participants who watched the video (step 1 of TACTIC)	5
		Dates, numbers, percentage of attendance, and number and content of advice of multidisciplinary meetings (step 2 of TACTIC).	5
		Dates, percentage of attendance, and content of individualized treatment plans of shared decision visits (step 3 of TACTIC).	5
		Date of follow-up visit with the nurse, and type of advice followed up or executed.	5, 10, 15, 20
		Nurse mental health or nurse CVR case manager.	5
		Numbers and reasons for drop-outs.	0, 5, 10, 15, 20
		Numbers and types of (serious) adverse events.	0, 5, 10, 15, 20
Costs of intervention	Health utilization questionnaire	Healthcare utilization is measured with the Dutch version of the Treatment Inventory of Costs in Patients with Psychiatric Disorders (TIC-P) questionnaire(38).	0, 5, 10, 15, 20
	EMR, finance, and correspondence	Costs related to health care, such as medication, visits to the general practice, and visits to relevant medical specialists.	0, 5, 10, 15, 20

AAPs, atypical antipsychotics; APs, antipsychotics; EMR, electronic medical records; GP, general practitioner; HDL, High-Density Lipoprotein.

Appendix A3. The sample size calculation formula

The standard deviation of the difference in QRISK3 score was 3.4 and the standard deviation of a single measurement was twelve. This means there is a high (test-retest) reliability r_s on the patient level, calculated via the relation:

$$\boldsymbol{rs = 1 - (SDdiff/SD)^2 \ / \ 2 \approx 0.95}$$

Appendix A4. Economic evaluation

The standard cost prices from the 'Dutch Guidelines for Cost Analyses' and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real cost prices will be determined based on full cost pricing. In the end, volumes of care will be multiplied by the cost prices for each volume of care to calculate costs.

Ultimately, the incremental costs will be related to the incremental QALYs expressed by the incremental cost-utility ratio (ICUR). Due to the stepped wedge design of the study, a multilevel model with time as a covariate will be used to analyze net monetary benefit (NMB) values to estimate the Incremental NMB (INMB). To estimate the uncertainty surrounding the ICUR, this regression model will be bootstrapped with one thousand replications. Results will be presented as means with 95% percentiles, and graphically with a cost-effectiveness plane (raw data) and a willingness to pay (WTP) curve with varying WTP levels. Because the effects of better CVRM lie beyond what is possible to measure during the follow-up period of the trial, we will perform a second cost-effectiveness analysis in which costs and disutility related to cardiovascular events will be incorporated in a decision analytic modeling study. The QRISK3 score measured at the end of follow-up in this trial gives a patient a specific 10-year risk of CVD and will be multiplied by the cost and disutility related to specific cardiovascular events using a Markov Model(42). Also, the management of CVR with for instance statin use will be included in the model. The costs and disutility related to CVD will be derived from the established CE model in the field of CVRM published in the literature. The influence of parameter uncertainty in this model will be explored by probabilistic sensitivity analysis with a Monte Carlo simulation (n=1000).

Chapter 8

General Discussion



This thesis aims to examine the nature, extent, and challenges of cardiovascular risk management (CVRM) in primary healthcare for patients with severe mental illness (SMI) from the perspective of GPs. Furthermore, this thesis aimed to outline the development of TACTIC, an intervention to reduce preventable cardiovascular risk factors in patients on atypical antipsychotics and to prepare for trial testing its effectiveness. A new definition of SMI was used to become more applicable to primary care settings in the Netherlands. This definition includes:

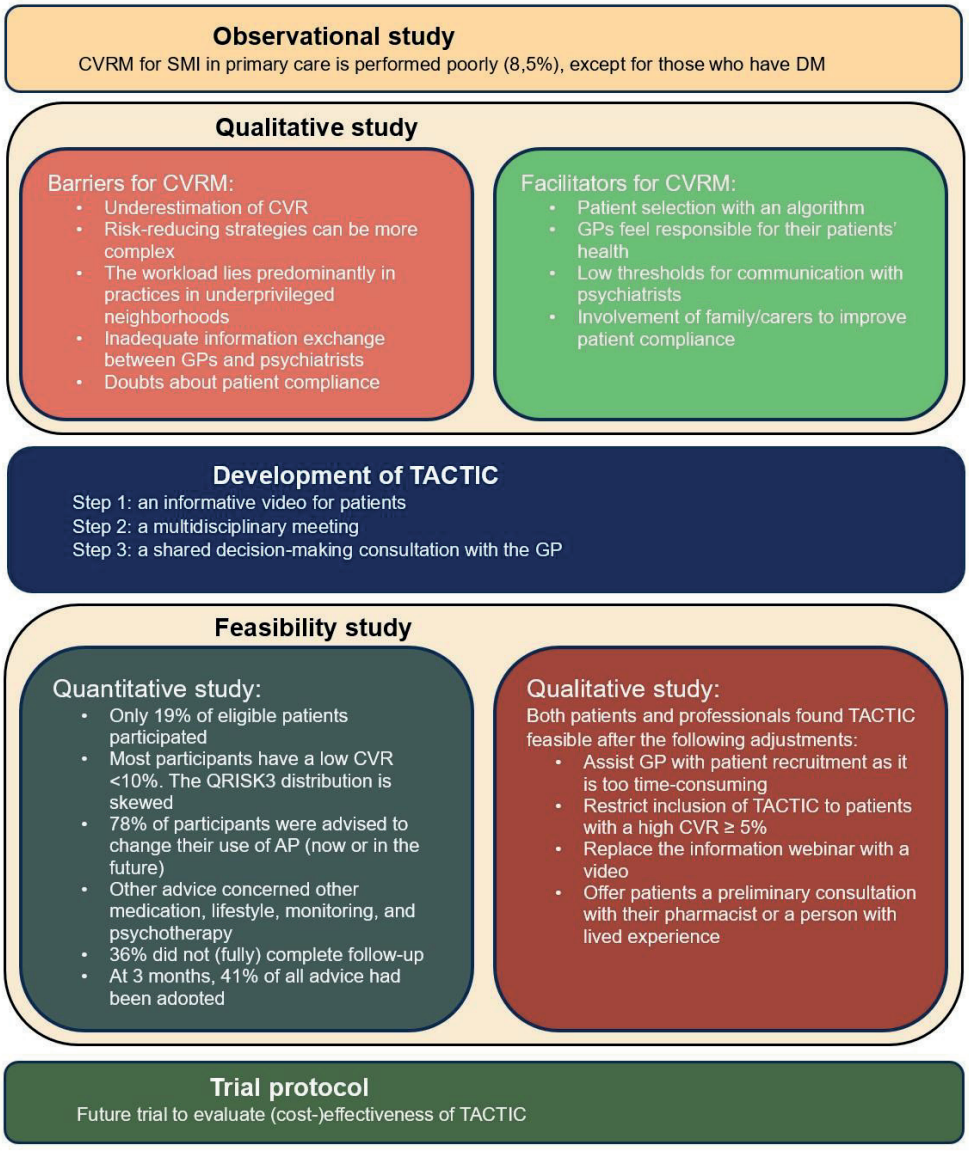
1. Schizophrenia;
2. bipolar disorder;
3. other psychosis or psychotic disorders;
4. the chronic use of lithium or antipsychotics (if not prescribed for delirium or dementia).

The editorial of Chapter 2 aimed to raise awareness about the increased cardiovascular risk (CVR) among healthcare professionals and urge them to consider a collaborative effort with the title: “It is time to take action”. The observational study described in Chapter 3 aimed to examine the rate of CVR screening in primary care patients with SMI and identify factors associated with adequate screening. The interview study described in Chapter 4 with general practitioners (GPs) aimed to provide insights into the barriers that need to be resolved and the facilitators that could improve the implementation of CVRM for this patient group. Additionally, an intervention was developed to effectively reduce preventable CVR factors, including the adverse effects of antipsychotics. At the beginning of this development process, we presented our findings and insights to a regional group consisting of general practitioners, nurses, psychiatrists, pharmacists, and persons with lived experience. This inspired them to create and test a collaborative care intervention[1], called TACTIC (**T**ransmural collaborative care model for CVRM and medication review for patients using **A**ntipsy**C**ho**TIC**s). The feasibility study described in Chapters 5 and 6 was conducted to prepare for a future trial of which the protocol was outlined in Chapter 7. In the previous Chapters, the main findings, merits, and limitations of the studies presented in this thesis have already been discussed in detail. This chapter provides a general overview of the main findings, compares them with recent literature, highlights methodological considerations, provides recommendations for general practice, primary care cooperatives, (CVRM) guideline developers, and policymakers, and suggests directions for future research.

Main findings.

The main findings of the studies presented in this thesis are summarized in Figure 1.

Figure 1. Main findings.



AP antipsychotics, CVR cardiovascular risk, CVRM cardiovascular risk management, DM diabetes mellitus, GP general practitioner, SMI severe mental illness, QRISK3 risk calculator of the UK National Health Service, TACTIC transmural collaborative care model for CVRM and medication review for patients using antipsychotics.

The observational study revealed that the high cardiovascular risk in patients with an SMI is often overlooked in primary care. Only 8.5% of these patients were adequately screened for CVR when they did not also have diabetes mellitus (DM) or cardiovascular disease (CVD). A diagnosis of DM or CVD increased the screening rates to respectively 68.4% and 26.7%. The distribution of the 1150 patients on AP with a diagnosis of schizophrenia, bipolar disorder, or psychosis, and those without was 32% and 68% respectively.

The qualitative study revealed that the participating GPs felt responsible for their patients' health, but they were often unaware of the increased physical risks and did not feel confident dealing with the adverse metabolic effects of antipsychotics. Psychiatrists and GPs did not collaborate enough to reduce cardiovascular risk because they did not exchange information about CVRM. GPs had doubts about patient compliance with annual checkups.

The feasibility of the TACTIC intervention was examined in Chapters 5 and 6 by using both quantitative and qualitative methods. The intricate process of implementing TACTIC was studied, various outcome measures were tested, and numerous experts were engaged to explore potential ways to trial-test the (cost-)effectiveness of CVR reduction. Participation in the intervention was restricted to patients using atypical antipsychotics, as these medications are associated with a greater expected reduction in cardiovascular risk compared to classical antipsychotics.

In the quantitative section of the study testing TACTIC's feasibility, the results demonstrated promising effects. Three months after the intervention, the participating patients had adopted 41% of the advice provided, resulting in a significant improvement in their CVR. This improvement was partly achieved because four out of ten smokers had successfully quit smoking. The number of eligible patients who participated was significantly lower than anticipated, and 36% of them did not complete the follow-up visit three months after the intervention.

In the qualitative part of the feasibility study of TACTIC (Chapter 6), the experiences and opinions of patients and healthcare professionals involved in the study were examined. Both groups concluded that, with some adjustments, TACTIC could be feasibly implemented. Inviting participants for the trial by time-pressed GPs will require support from the research team due to the pressure of inviting enough participants simultaneously. TACTIC was found

to be most beneficial for patients with a high CVR, as discussions during multidisciplinary meetings were more productive.

The trial protocol outline incorporates lessons learned from the previous studies. It describes the incomplete stepped wedge cluster randomized design, using two primary outcomes, namely cardiovascular risk and mental health as measured with the QRISK3 score and MHI5, respectively.

Based on the findings, we concluded from the studies described in this thesis, that CVRM for patients with an SMI in primary care requires improvement. The process can often be too complex for GPs to handle effectively without the assistance of psychiatrists, especially when antipsychotic medications lead to adverse metabolic effects or complicate smoking cessation efforts. Additionally, engaging patients in their own care can be challenging. However, when patients do become involved, they can significantly enhance their health outcomes.

Comparison with recent literature

Although studies about SMI in primary care are generally scarce, a few studies have been published during the past few years relevant to our findings. These will be discussed in six sections: Prevalence of SMI, poorly performed CVR screening, off-label prescribing of antipsychotics by GPs, barriers and facilitators perceived by GPs concerning CVRM, interventions to enhance CVRM for SMI in primary care, and persons with lived experience.

Prevalence of SMI

In the past three decades, studies have shown a life expectancy gap ranging from 10 to 25 years between patients with an SMI and the general population, mainly due to cardiovascular diseases[2-5]. The wide variation is due to the different definitions of SMI[6]. We found a prevalence of 1.5% in 2013-2015 in our GP-based registration database. According to healthcare costs paid by health insurers, the prevalence of patients with an SMI has not changed from 2015 until 2019[7]. The definition used in the data from the health insurers refers to individuals who have received treatment in specialized mental healthcare at least once in the past three years for schizophrenia, are currently on antipsychotic medications or lithium, are institutionalized in a mental healthcare facility, or have received annual treatment in

specialized mental healthcare for a chronic mental disorder for at least three years. The estimated number of affected adults is 218,200, which includes 41,000 new patients and 41,000 individuals transitioning out of care each year[7]. According to data from health insurers, there are approximately 191,500 patients with an SMI who are not institutionalized, representing about 1.4% of the adult population in the Netherlands. The definition of SMI used in this thesis encompasses a slightly broader group of patients, leading to an estimated prevalence of 1.5%. The observed difference may be due to regional variations, the presence of uninsured individuals, or patients who are not taking antipsychotics or lithium and have not received specialized mental healthcare, yet still meet the diagnosis criteria.

Poorly performed CVR screening

The higher risk of cardiovascular disease is attributed to various factors such as unhealthy lifestyle, stress from mental illness, and its social consequences[8-13]. Recent studies show that the reported gap in excess mortality has increased since 1990[14,15]. The increase is thought to be caused by the growing use of atypical antipsychotics, which can have negative metabolic effects(15). This highlights the importance of screening for risk factors and providing cardiovascular risk management for those with a high CVR.

CVR screening is performed poorly in Dutch primary care as described in Chapter 3. This contrasts with the United Kingdom's screening rates, which are now significantly higher than those in the Netherlands. Already in 2016, the UK government recognized the barriers that patients with an SMI face in accessing physical health checks, and invested in an SMI register with financial compensation for GPs to boost screening rates. The government funded research on this topic, and since 2018 the NICE guidelines provide clarity on how the additional CVR should be evaluated[16]. In addition, in 2019, the NHS introduced a five-year mental health implementation plan, which offers guidance for local areas on how to achieve mental health goals, and the improvement of screening rates was one of the goals[17]. At the end of 2023, 361,210 out of 527,556 (68%) people on the General Practice SMI register had received a full and comprehensive physical health check in the preceding 12 months[18]. These high screening rates show what can be achieved if the problem is addressed nationally.

Off-label prescribing of antipsychotics by GPs

Another important finding of our observational study (Chapter 3) was a high percentage of patients using antipsychotics who did not have a diagnosis of schizophrenia, bipolar disorder or psychosis, namely 68% of AP users. We initially believed that several factors might have caused this issue: GPs prescribing antipsychotics for off-label use, a lack of information about the diagnosis, or errors in coding. An article by Cinar et al., suggests that the high percentage of AP users without an SMI diagnosis was mostly caused by the frequent off-label prescribing and less by the wrong coding[19]. In this study, information about the reason for prescribing was explored from electronic medical files in six Dutch general practices for 303 new quetiapine users. 76.6% were prescribed to patients without a diagnosis of SMI, and 47% had a sleep disorder often with comorbidity of a mental disorder other than SMI. Antipsychotics with sedative properties may be prescribed to replace benzodiazepines to prevent addiction; however, the Dutch guideline on sleeping disorders in 2024 advises against this practice[20]. Another reason might be that the benzodiazepine reimbursement was discontinued in 2009[21]. Furthermore, pharmaceutical companies like AstraZeneca and Eli Lilly and Company have marketed off-label prescriptions for quetiapine and olanzapine[22,23]. Quetiapine is the most commonly prescribed atypical antipsychotic off-label (in terms of users), followed by olanzapine and risperidone[24,25]. One might think that only a high dosage can cause cardiovascular disease. However, recent evidence suggests that even a low dosage of quetiapine (≤50mg) can cause cardiovascular disease[26]. Moreover, many other adverse effects are very commonly associated with low-dose atypical antipsychotics: Daytime sedation ('hangover') is frequently reported for quetiapine[27]. Other observed adverse effects include restless legs, dry mouth, and impaired attention. Underestimation is likely to occur if these adverse effects are not regularly monitored.

Barriers and facilitators perceived by GPs concerning CVRM

CVRM guideline

A lack of awareness and knowledge about the additional cardiovascular risk was identified as a significant barrier to CVRM for patients with an SMI (Chapter 4). It could be beneficial for the existing CVRM guidelines for GPs to specifically address the need for monitoring risk factors in patients with an SMI. For instance, in Australia, SMI is a built-in reclassification factor in the CVR estimation tool of the 2023 CVRM guideline[28]. This is also the case in the UK NICE

guidelines, which even offer guidance on who to screen, by whom, and in which frequency[16,29,30]. In the latest update of the Dutch CVRM guideline in 2024, SMI is mentioned for the first time as a reason to consider CVR assessment[31]. It is stated that having an SMI might be an independent risk factor that is not considered in the European risk assessment tool (SCORE2). To get around this, it is recommended to use QRISK3 for a more accurate risk assessment. One may find the wording overly cautious, likely due to the strict following of GRADE criteria[32]. While there is more evidence available, for example, regarding the reclassification properties of a coronary calcium score, what about the increasing health disparity for patients with an SMI? This specific group of patients is often described to be vulnerable, "hard to reach", and suffering from stigma by health professionals[33]. Research on primary care populations often overlooks certain groups, leading to a lack of knowledge about the feasibility and effectiveness of interventions for these populations. As a result, existing guidelines offer limited and conflicting guidance on their specific health risks. As noted in Chapter 1, the Dutch multidisciplinary guideline for the care of individuals with severe mental illness, published in 2017, recommends annual check-ups[34]. However, policymakers and health insurance companies refer to the CVRM guideline to determine which types of care will be funded. As a result, annual screenings for CVR in primary care are not accessible for patients with an SMI unless they also have another diagnosis, such as hypertension, hypercholesterolemia, CVD, or DM. This creates a loop of reasoning that perpetuates the problem, making it difficult to find a solution. Commissioned by the Dutch Zorginstituut, an advisory board for the Ministry of Healthcare named Equalis emphasized the need to reduce health disparities[35]. Their report recommends, among other things, to improve equity in guidelines through the deployment of a stratified selection of subjects with different SES and ethnic backgrounds. In some countries, committees and panels are employed to consistently address relevant health equity considerations when developing guidelines for chronic diseases[36]. Such a panel could, for instance, consider which patient groups are underrepresented in research, although they are overly represented in having the chronic disease discussed in the guideline, to complement GRADE's evidence-to-decision framework. Researchers like Akl and colleagues advise the following three steps[37]:

- Train representatives of disadvantaged populations to be involved in both the content and the process of guideline development.

- Use a structured format to facilitate the active participation of representatives of disadvantaged populations and their provision of valuable feedback.
- Include a section in reports of equity-sensitive guidelines that details any lack of evidence relating to relevant disadvantaged populations

CVRM is considered complex when antipsychotics are involved

The GPs interviewed in our study indicated that they often continue prescribing antipsychotics initiated by a psychiatrist for many years without understanding the rationale, and feel unable to change it (Chapter 4). This finding was endorsed in a qualitative study by Woodall, who described patients in primary care becoming 'trapped' on antipsychotics, due to inhibiting opportunities to deprescribe. GPs felt unsure about managing antipsychotic medications without assistance, and both GPs and psychiatrists expressed concerns about being held responsible if something harmful happened after stopping the medication, which inhibited deprescribing[38].

Another barrier GPs described was the difficulty of implementing risk-reducing strategies when a patient is using antipsychotics due to a lack of knowledge. The most effective way to reduce CVR is smoking cessation. Although patients with an SMI are as motivated to quit as the general population[39], smoking cessation rates are lower[40]. A Cochrane review challenges the theory that smoking serves as self-medication. It indicates that mental health does not deteriorate after quitting smoking. There is low to moderate certainty evidence suggesting that smoking cessation is linked to small to moderate improvements in mental health[41]. These findings have not yet reached all mental health providers. In a survey, it was found that only a small percentage offered advice or support for quitting smoking[42]. The barriers identified included a lack of training among providers and a belief that patients were not interested in cessation. Pharmacologically, smoking cessation can be more complex due to interactions between antipsychotics and smoke or contraindications of medication used against craving for patients with SMI. The soot from smoking can interact with some antipsychotic medications, potentially lowering their effectiveness. Some patients may use smoking to alleviate the adverse effects of these antipsychotic medications[43], and smoking cessation can significantly impact clozapine blood levels[44]. Furthermore, there is no guidance

provided on options to support smoking cessation for patients with an SMI. The recently updated Dutch guideline on smoking cessation still states that bupropion and varenicline should not be prescribed to patients with an SMI[45]. This makes it more difficult for patients with an SMI to quit smoking. There is evidence that these medications can be used safely: Two reviews cited numerous references supporting the safe use of bupropion and varenicline for smoking cessation in individuals with an SMI[46,47]. In our feasibility study of the TACTIC intervention (Chapter 5), 40% of users had successfully quit smoking 3 months after using TACTIC. The future trial, (protocol described in Chapter 7), will determine if this success rate can be replicated with more patients. Smoking cessation will be discussed in the multidisciplinary meetings if relevant, and all experts can help address the challenges mentioned above.

An additional challenging risk-reducing strategy as encountered during the TACTIC intervention involved a patient with a combination of an SMI, diabetes, and impaired glucose regulation due to the use of olanzapine. Most GPs and psychiatrists agree that the treatment of diabetes for patients with SMI is the responsibility of the GP[48]. However, this situation illustrates the necessity of a collaborative effort to make difficult decisions. Together, they can explore options such as increasing blood glucose-lowering medications or switching the olanzapine to an antipsychotic that has fewer metabolic side effects, such as aripiprazole.

The role of informal caregivers

An important facilitator mentioned by the general practitioners in our interview study was the involvement of spouses, family members, and other informal caregivers in CVRM (Chapter 4). During the feasibility study, informal caregivers rarely participated in the multidisciplinary meetings, even though their involvement in TACTIC was highlighted as important for the patients. In interviews, patients were asked about the role of their caregivers, as discussed in Chapter 6. Their responses were mixed; while they recognized the positive impact of caregiver involvement, they also voiced concerns about losing their autonomy. Additionally, many felt that spouses often carry a significant burden and should not be overstretched. A recent review on family involvement in supporting cardiovascular self-management for individuals with an SMI highlighted the complex role caregivers play in helping the person maintain both the 'self' and the 'management' aspects of their condition. Caregivers often expressed their dedication to this role and highlighted the significance of being part of the patient's integrated treatment

plan[49]. Caregivers found it challenging to address the individual's risky health behaviors, such as smoking. They acknowledged prioritizing the person's mental health over their cardiovascular health. Despite knowing the harm smoking could cause to the individual's physical well-being, they provided cigarettes to help cope with mental health symptoms[50]. These findings led us to conclude that having informal caregivers present during TACTIC, along with their understanding of the rationale behind the advice given, is beneficial. In the protocol of our future trial (Chapter 7), the importance of informal caregivers has been emphasized, while also respecting the patients' autonomy when inviting patients.

Interventions to enhance CVRM for SMI in primary care

According to the Medical Research Council, an intervention becomes more complex with[51]:

- a high number of intervention components and the interactions between them.
- a high range of behaviors, expertise, and skills (e.g. particular techniques and communication) required by those delivering or receiving the intervention.
- difficult organizational levels or settings that are targeted by the intervention.
- a need for a high level of flexibility or tailoring of the intervention or its components.

Our intervention TACTIC, as described in Chapters 5, 6, and 7 was designed as a complex intervention that included multiple components and required tailoring for each patient. The complexity was amplified at the organizational level due to the collaborative effort of various professionals, as well as the challenging nature of the patients, who can be difficult to engage.

We found only three other interventions specifically aimed at improving CVRM for patients with SMI in primary care:

i. In a UK study, the (cost-) effectiveness of the Primrose intervention for patients with SMI and high cholesterol was evaluated[52]. The Primrose intervention can be described as an intensified CVRM program: 8-12 appointments with a nurse over 6 months. 76 GP practices were randomly assigned to the intervention or treatment as usual (TAU). A total of 69% of patients attended two or more appointments. The analysis showed no difference in the primary outcome, the cholesterol levels at 12 months between the two groups. The effect was

probably diluted due to the evaluation of the lipid profile for the study in the TAU group, which prompted the start of lipid-lowering therapy.

ii. The SOFIA project developed a patient-centered care approach for GPs in Denmark[53]. The intervention comprised extended structured consultations carried out by the GP, group-based training of GPs and staff, and a handbook with information on signposting patients to relevant municipal, health, and social initiatives. In the feasibility study, five general practices attempted to contact 57 patients with SMI. Of these, 38 patients (67%) attended an extended consultation, which led to changes in the somatic health care plan for 82% of patients. This was followed by a pilot RCT among 9 practices[54]. The extended consultations were delivered with a high level of fidelity in the general practices. However, thresholds for collecting outcome measures and recruitment of practices and patients were not reached. The flow chart of their patient recruitment process had a lot of similarities with ours in the feasibility study described in Chapter 5. In the SOFIA pilot study, like in ours, an algorithm was used as a digital tool assisting the GPs in performing the patient eligibility assessment. The advantage of an algorithm is that it selects based on the criteria without trying to be discreet. The GPs might disagree with this lack of discretion in patient selection and therefore skip patients on the list. In the SOFIA pilot trial, the different understandings of what defines an SMI burdened the GPs in their assessment. The GPs were interviewed about the process of patient recruitment. Important findings were that GPs protect the practice and the patient when assessing patient eligibility, being familiar with the patient was important for successful recruitment, and the GPs were hesitant to recruit patients they thought would not be compliant. The downside of using algorithm-generated lists in research can be that if GPs remove patients from the list because they deem them unsuitable or ineligible, the researchers lose the overview. Advice from a systematic review of patient recruitment strategies in primary care research highlights the importance of enlisting the support of healthcare practitioners. As they serve as gatekeepers to both services and patients, it is essential for researchers to effectively communicate the value of the proposed research and gain their support[55].

iii. The third study used a clinical decision support tool among clinicians and patients of 78 primary care clinics in the USA[56]. The tool provided a summary of modifiable CVR factors and personalized treatment recommendations. Intervention patients had a significant 4% relative risk reduction in total modifiable risk compared to controls in 12

months. In this study population, the absolute CVR was 9.1% and therefore the decrease was on average 0.36%. The setting was a clinic where general practice and specialist mental healthcare were integrated. In the Dutch healthcare system, this could be a beneficial intervention for mental healthcare institutions and could be implemented during patient visits.

The interventions mentioned above are focused on a single discipline and aim to give GPs or nurses more opportunities, information, and awareness to address cardiovascular risk management (CVRM). Research shows that a collaborative care model can effectively address both mental disorders and somatic comorbidity[57-59]. Collaborative care could be practical when the care needs are complex and require a tailored holistic assessment. As far as we know, TACTIC is currently the only intervention intended to promote collaboration among patients, GPs, and psychiatrists to reduce cardiovascular risk.

Persons with lived experience

Persons with lived experience can help patients find their purpose and reduce self-stigma. This support is essential for CVRM. If a patient does not see their life as meaningful or enjoyable, why would they want to adopt a healthier lifestyle? Enhancing various aspects of life, such as living, working, learning, and maintaining social relationships, is a process known as 'recovery'[60]. A recent survey of Dutch patients with SMI found that only 57% felt somewhat included in society[35]. The involvement of persons with lived experience for recovery purposes is a relatively new concept for GPs, unlike their engagement in research settings[61] and clinical environments within specialist mental healthcare[62]. Throughout our studies, we collaborated with twenty individuals who had personal experience with mental health issues, from the initial design phase to the TACTIC trial preparations. Their task in the TACTIC intervention was to motivate patients to actively participate in their treatment, empower them, ask about any complex terminology used by professionals, and offer information on local community programs for recovery care. The only requirement for selecting these persons, aside from being clinically stable, was that they had completed a course for coaching as a person with lived experience in SMI. The individuals were found through organizations of experts with lived experience in Arnhem, Nijmegen, Deventer, Utrecht, Amsterdam, and Rotterdam. They were compensated for their time and expertise.

According to Jones et al., persons with lived experiences may find it challenging to integrate into an institutional setting with its existing customs, norms, and cultures. These feelings can stem from a lack of guidance and planning, which can lead to confusion over job duties and responsibilities[63]. This was the case for the persons with lived experience in our team, as mentioned in Chapter 6. They found it challenging to contribute to the conversation during the meetings (step 2 of TACTIC) because it was their first encounter with the participating patients. Unlike the psychiatrist, who had received information about the medical details in advance, this meeting marked their initial engagement with the patients, making it more difficult for them to assume their roles effectively.

Including them in our study team and having them directly collaborate with the participants proved to be beneficial in many ways. Their feedback led to numerous changes in the trial protocol. For example, they provided valuable input on inviting patients, the wording of the patient information documents, and the introduction of a baseline visit for each participating patient who wished to prepare for the meeting together. Their presence was also greatly valued by healthcare professionals. In our focus group meeting (Chapter 6**)**, healthcare professionals described them as a supportive "sidekick" for participants going through similar experiences.

Other authors suggest that involving persons with lived experience in research and healthcare is especially important when working with vulnerable patient groups who face stigma. Many publications focus primarily on studies of interventions for groups such as homeless individuals[64], refugees[65], patients with cognitive or social disabilities[66], and those with an SMI[67,68]. These studies generally found that including patients in the research process was challenging, and acknowledged the potential benefits of leveraging lived experience in both the process and the interventions. Furthermore, individuals with lived experience can play a crucial role in reducing stigma within healthcare settings[69].

Methodological considerations

The incomplete stepped wedge design

In Chapter 7, we outlined the protocol for our upcoming trial to assess the (cost)effectiveness of TACTIC. Assessing the health impacts of a complex intervention like TACTIC is challenging as mentioned above[51]. First, there are many organizational challenges due to the involvement of different general practices and multiple professionals, which require a lot of communication

and coordination. Second, the patient group presents unique challenges because they are often difficult to reach, unable or unwilling to participate in studies, and follow-up can be problematic[54,70,71]. Third, the risk to individual patients depends on personal circumstances and requires customized care, making it difficult to measure a general health effect. We used the Medical Research Council framework for the development and evaluation of complex interventions as guidance to deal with these challenges[51]. The framework recommends conducting a feasibility study, which we agree is a crucial step in the process of constructing and preparing for the trial. We chose the stepped-wedge design instead of a standard parallel two-arm trial with intervention and control groups because, due to repeated measurements and ultimately involving everyone as an intervention participant, we could manage with fewer patients. Furthermore, it was more practical not to have all practices start the intervention at the same time. The reason for choosing an 'incomplete' stepped wedge trial design was the ethical problem of patients with an established high CVR who are withheld from treatment due to their GP's randomization in a standard stepped wedge design. For instance, if a patient is part of a cluster that will start the intervention in the last wave, according to a complete format with a total follow-up time of 20 months starting from baseline, the time between their first CVR screening and treatment of the risk factors would be 15 months. In the incomplete format, participants will receive the intervention immediately after their first (baseline) CVR screening. Furthermore, the risk of 'contamination' in the control group, as observed in the Primrose study[52], is lower. After all, the patients continued care as usual until the moment of inclusion where care as usual often did not include CVRM. Other researchers who used this incomplete design[72-74] also reported that it improved the efficiency of the study and that the stepped wedge design enabled a more gradual and manageable implementation of the study protocol and data collection[72]. However, one drawback mentioned is that a long lead-in time for professionals randomized in the last wave may lead to decreased motivation and engagement by the time study activities begin[74].

Strengths and limitations

The strength of the TACTIC intervention is that it was developed through a multidisciplinary collaboration of professionals and patients who plan to implement it themselves. This increases its likelihood of being successfully implemented compared to a top-down design.

The approach aligns with the core values of Dutch general practice, which emphasize being medically comprehensive, person-centered, collaborative, and continuous. Additionally, it aligns with the recommendations outlined in a national vision document for primary care for patients with mental health issues, stating that CVRM is necessary for patients with SMI[75].

Another strength of this thesis is that our research team greatly benefited from an advisory group comprised of experts in various fields. This group included specialists in qualitative research, conduct and statistics of cluster randomized trials, and intellectual disabilities, as well as a pharmacist who focuses on psychotropic medications, and psychiatrists. Additionally, representatives from Anoiksis, a national organization for individuals at risk of psychosis, and MIND-Ypsilon, a national organization for family members of individuals with SMI, contributed their expertise. The advisory group played a key role in designing research on TACTIC and was consistently updated on the progress.

This thesis also has some limitations. First, it is embedded in the Dutch primary care model (Chapters 3 to 7), which may limit its applicability to other contexts. However, the findings and recommendations can be valuable for other countries with similar primary care structures, improving cardiovascular risk management and prescribing antipsychotics according to established guidelines. Moreover, the global challenge of bridging the gap between somatic and mental health care suggests that other nations are likely to face many of the same issues discussed in these studies. They may therefore benefit from our experiences and make adjustments depending on their setting.

A second limitation concerns the definition of SMI used in our studies. It included patients who were prescribed antipsychotics but did not have a correctly recorded diagnosis of schizophrenia, bipolar disorder, or psychosis. This definition was selected to ensure it was more relevant to primary care settings and to avoid excluding patients with an SMI who might have been misclassified due to incorrect coding in their electronic medical records. However, the aforementioned mortality gap of 15-25 years due to CVD may not apply to them, and the use of this definition has led to an overestimation of the prevalence of SMI. We conducted an additional analysis to compare the CVR screening rates of patients on antipsychotics with an SMI diagnosis with screening rates of patients on antipsychotics without an SMI diagnosis, resulting in rates of 7.3% for the first and 9.7% for the second group. This indicates that both

groups rarely receive screening despite being at risk for CVD. Off-label antipsychotic users may also encounter negative metabolic adverse effects as atypical antipsychotics are an independent CVR factor. Additionally, for patients who have never experienced a psychotic episode, tapering off antipsychotics is generally less risky. Therefore, we thought it beneficial to include these patients on atypical antipsychotics in the TACTIC intervention.

Recommendations

General practice

In the study described in Chapter 4, an algorithm was used to identify patients with an SMI or those taking atypical antipsychotics who had not received their annual CVR screening. This algorithm provided the GP with immediate insight into which patients were lacking CVRM and helped to assess the amount of work needed to organize their care. The annual use of such a patient selection tool could be very helpful to the GP for regular mapping of this specific patient population.

Delivering TACTIC may require less time and effort for individual GPs than during a trial, as patients can be approached gradually. However, this process will require support from the regional primary care cooperative to handle the organizational tasks previously managed by the research team.

In Chapter 1, Mrs. D.'s case was introduced to illustrate the questions and dilemmas a GP could face. Now, the potential benefits will be demonstrated if she participates in TACTIC.

I plan to discuss with her the potential impact of olanzapine on her body weight during her next visit. I'm unsure how this can be alleviated, but I will inform her about the TACTIC program and invite her to participate once I have spoken to a few more interested patients. If she would like to participate, we could work together to create a plan with the help of the psychiatrist, someone with lived experience, and my nurses. The group will likely advise her to consider discontinuing the antipsychotic medication, as olanzapine can lead to weight gain and the risk of a psychotic episode appears to be very low. The psychiatrist will guide us on how to gradually reduce the dosage, specifying the number of milligrams to be reduced over a certain number of weeks. If Mrs. D decides to taper the olanzapine off, we can also arrange for weekly visits to the mental health nurse, who is also part of my practice, to provide support

during the transition. Furthermore, the psychiatrist will provide us with a backup plan to start an alternative medication if she becomes unstable. If I have any questions about her situation in the future, I can use the digital consultation for updates, just like we did when we prepared the meeting to inform the psychiatrist in advance. Additionally, Mrs. D. may be interested in activities organized by a local organization for people with lived experience. Our representative with lived experience will introduce this option to her. After TACTIC, she understands the benefits of joining the CVRM program. The nurse will understand her needs and monitor her at least annually. Now she has connected with a network of people who can support her.

Primary care cooperatives

Primary care cooperatives in the Netherlands have a unique opportunity to facilitate communication between primary care, specialist mental healthcare, and welfare. In our preparations for the TACTIC trial, we found that primary care cooperatives often support digital communication tools and facilitate the sharing of medical health records between GPs and psychiatrists. They have the network and the experts on chronic care and mental health to improve CVRM for patients with SMI. If the TACTIC trial proves its effectiveness, the primary care cooperatives may play a pivotal role in assisting their GPs by organizing this collaborative care intervention.

CVRM guideline development process

The most recent update of the Dutch CVRM guideline does not explicitly state that screening of people with an SMI is necessary to reduce mortality due to cardiovascular diseases[31]. This is inconsistent with the Dutch multidisciplinary guideline for the care of people with SMI, which recommends annual screening[34]. These guidelines should be aligned to ensure consistent recommendations for screening practices. Furthermore, confusion about the risk assessment can be resolved if both sets of guidelines endorse the use of QRISK3 for patients with an SMI.

In the future, guidelines should be developed in a more person-centered approach, with close collaboration from patients. This aligns with the recommendations of the Quality Council of the Healthcare Institute[35].

Priorities for future research

Comparison of treatments for sleeping disorders with comorbid mental disorders

Sleeping disorders are a public health burden and often occur in combination with mental disorders as comorbidities. GPs often initiate quetiapine to treat sleeping disorders, particularly for patients with coexisting mental health problems. This approach may be used to avoid the prescription of benzodiazepines. However, there is generally a lack of awareness regarding the adverse effects of quetiapine[76]. In contrast, GPs tend to be more informed about the negative effects associated with benzodiazepines, which include cognitive impairment, tolerance, rebound insomnia upon discontinuation, increased risk of accidents and falls, and the potential for abuse and dependence[27]. Consequently, the clinical use of off-label drugs and novel drugs that do not target the GABAergic system is increasing[27]. Several alternative treatments are available with different pharmacological profiles and mechanisms of action. These include melatonergic agonists, the H1 antagonist low-dose doxepin, and various histamine and serotonin receptor antagonists such as amitriptyline, mirtazapine, trazodone, olanzapine, and quetiapine[27]. Further research is needed to compare the effectiveness of these medications for sleep disorders, especially when comorbid mental disorders are present.

What about the young?

A recent meta-analysis estimated that patients with an SMI have over twice the odds of physical multimorbidity compared to those without, especially among those aged 40 and younger[77]. This highlights the need for early intervention. The TACTIC intervention may not be appropriate for patients with low cardiovascular risk who are taking atypical antipsychotics, as they may have low motivation for managing their cardiovascular risk, leading to less effective meetings. Our feasibility study found that setting the limit at a QRISK3 of 10% would result in excluding all young people due to the strong correlation between the risk estimate and age. Yet research shows that young people on atypical antipsychotics do have significant metabolic abnormalities[78,79]. This indicates that this group should be monitored and treated more intensively than is currently the case. Research indicates that young people are often more motivated by physical appearances than by having a high CVR[80]. Furthermore, there is a study on interventions where young patients with SMI received health coaching in groups or individually, along with activity tracking and popular technologies, using mobile phones[81]. A

clinically significant CVD risk reduction, weight loss, and cardiorespiratory fitness were achieved after 6 and 12 months. Future research should teach us what intervention could be useful for monitoring the CVR of the young. So far, we have not found any interventions in primary care addressing this topic.

Proactively invite patients for CVR screening, what works?

In our feasibility study, as well as in all three interventional studies mentioned above, it was very challenging to include and retain patients. How can we encourage the large group of patients with serious mental illness (SMI) in primary care to prioritize their physical health more effectively? There is limited evidence available on this topic[38]. Future research focused on understanding patients' perspectives could help tailor the approach to inviting them, potentially leading to higher participation rates and increased effectiveness of CVRM initiatives.

Conclusion

The CVR of patients with an SMI is systematically overlooked and requires a proactive approach in primary care. Moreover, if patients have high CVR and are taking atypical antipsychotics, simply including them in the existing CVRM programs will not be sufficient. Firstly, many patients with an SMI in primary care are unaware of their increased CVR, making it challenging to engage them on the topic. Secondly, patients require personalized advice, but GPs often lack the knowledge and confidence to provide it, especially when it comes to atypical antipsychotics. To enhance the care for this patient group, it is crucial to provide support from liaison psychiatry, for instance with an intervention like TACTIC. The collaborative nature of TACTIC ensures that healthcare professionals get to know each other by contributing their expertise during multidisciplinary meetings. This interaction can foster improved collaboration among professionals, enabling them to address other challenging issues. This patient-centered and interprofessional approach, which aims to involve patients through multiple collaborative healthcare professionals, shows promise, but only if patients are reachable and motivated to evaluate their cardiovascular risk (CVR). If this is achieved, significant health improvements can be realized for patients with an SMI in primary care.

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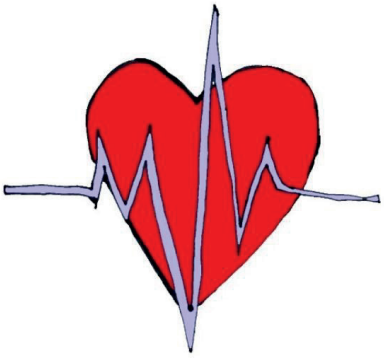
Chapter 9

Summary



This thesis aims to investigate the nature, extent, and challenges of managing cardiovascular risk (CVR) in primary healthcare for patients with severe mental illness (SMI) from the perspective of general practitioners (GPs), and to develop an intervention to reduce their CVR.

Chapter 1 provides a general introduction in which the definition of SMI is modified to be more suitable for the primary care setting in the Netherlands. This new definition includes:

- schizophrenia;
- bipolar disorder;
- other psychosis or psychotic disorders;
- the chronic use of lithium or antipsychotics (APs) if not prescribed for delirium or dementia.

The heightened CVR among individuals with an SMI often leads to a reduced life expectancy of 10-25 years compared to the general population. Cardiovascular disease (CVD) is identified as the primary cause of this disparity, driven by factors like antipsychotic medication side effects, unhealthy lifestyle habits, and systemic healthcare inequalities. Since the Dutch government transitioned SMI patient care from institutional settings to ambulatory care, GPs now play a critical role in managing these patients' overall health, including their CVR. However, despite this policy shift, most GPs are not fully equipped to monitor and treat CVR in SMI patients. The thesis investigates this gap and aims to develop an intervention to improve cardiovascular risk management (CVRM) in primary care.

Chapter 2 was published as an editorial. Its title was "It is time to take action." Its aim was to raise awareness among healthcare professionals about the increased CVR and urge them to consider a collaborative effort.

Chapter 3 presents an observational study that revealed that a high CVR in patients with an SMI is often overlooked in primary care in the Netherlands. Only 8.5% of these patients were adequately screened for CVR when they did not also have diabetes mellitus (DM) or CVD. A diagnosis of DM or CVD increased the screening rates to respectively 68.4% and 26.7%. A high frequency of visits, older age, the use of antipsychotics, and a diagnosis of COPD were also associated with a higher screening rate. The distribution of the 1150 patients on AP with a diagnosis of schizophrenia, bipolar disorder, or psychosis, and those without was 32% and 68% respectively. Further analyses indicated that the group with a diagnosis differed from those included due to using AP without a diagnosis in several ways. The percentages of women, patients taking antidepressants or CVR-lowering medication, patients with a

diagnosis of COPD, and patients who use tobacco, along with the number of visits to the GP, were all statistically significantly higher in the group of AP users without a diagnosis than in the group with a recorded diagnosis.

Chapter 4 provides qualitative insights gathered from interviews with GPs regarding their perceptions of CVRM in patients with an SMI. The study revealed that the participating GPs felt responsible for their patients' health, but they were often unaware of the increased physical risks and did not feel confident to change AP prescriptions. Psychiatrists and GPs did not collaborate enough to reduce CVR because they did not exchange information about CVRM. GPs had doubts about patient compliance with annual checkups. The chapter advocates for more robust communication channels, explicit guidance on risk assessment and management in the CVRM guideline, and training to improve primary care providers' confidence in managing CVR for this high-risk group.

Chapters 5, 6, and **7** detail the development and research related to the '**T**ransmural collaborative care model for CVRM and medication review in patients using **A**ntipsy**C**ho**TIC**s' (TACTIC). This intervention was created through a collaboration involving general practitioners, nurses, psychiatrists, mental health institution staff, individuals with lived experience, and representatives from the municipality in the region of Arnhem. The objective of this group was to enhance collaboration in the care of SMI patients using insights from our studies. They developed and conducted preliminary testing of the TACTIC intervention process with funding from ZonMw. Participation in the intervention was restricted to patients using atypical APs, as these medications are associated with a greater expected increase in CVR compared to classical APs. TACTIC is a one-time intervention that occurs within a general practice setting and involves three consecutive steps:

1. Informing patients about the upcoming multidisciplinary meeting to motivate and prepare them (and their caregivers) for participation.
2. Conduct the multidisciplinary meeting, where a set of personalized treatment recommendations is provided, including guidance on the use of atypical APs and strategies for reducing other CVR factors.
3. Holding a shared decision visit to create a customized action plan based on the recommended treatment options.

Chapter 5 includes the quantitative section of the study testing TACTIC's feasibility. The results demonstrated promising effects. Three months after the intervention, the participating

patients had adopted 41% of the advice provided, resulting in a significant improvement in their CVR. This improvement was partly achieved because four out of ten smokers had successfully quit smoking. The number of eligible patients who participated was significantly lower than anticipated, and 36% did not complete the follow-up visit three months after the intervention.

Chapter 6 outlines the qualitative aspect of the feasibility study for TACTIC, focusing on the experiences and opinions of patients and healthcare professionals involved in the program. Both groups concluded that TACTIC could be feasibly implemented with a few adjustments. It was determined that TACTIC is particularly beneficial for patients at high CVR, as discussions in multidisciplinary meetings tend to be more productive in these cases. Additionally, it is important to improve expectation management for patients by providing them with a preliminary consultation with someone who has lived experience or with their pharmacist, to reduce the tension towards the intervention experienced by patients. However, since GPs often face time constraints, they will need support from the research team to ensure that enough participants can be invited simultaneously.

Chapter 7 details the trial protocol and integrates lessons learned from the feasibility study. The goal is to evaluate the (cost-)effectiveness of TACTIC. After thorough consideration, an incomplete stepped wedge cluster randomized design was selected, utilizing two primary outcomes: cardiovascular risk, measured by the QRISK3 score, and mental health, assessed with the MHI-5.

Chapter 8, the general discussion, synthesizes findings from the previous chapters, comparing them with recent literature and outlining recommendations for improving CVRM in primary care for patients with an SMI. The key conclusions indicate that the prevalence of SMI in primary care is approximately 1.5% of the adult population. CVR screening is not being conducted effectively in the Netherlands for this patient group, unlike in the UK. Furthermore, GPs frequently prescribe APs off-label, particularly for sleep disorders associated with psychiatric comorbidities. Other interventions aimed at enhancing CVRM for SMI in primary care have all faced similar challenges in patient inclusion and adherence, highlighting the need to promote interdisciplinary teamwork. The involvement of persons with lived experience has proven valuable due to their unique perspectives, which enhance patient engagement. Other studies have also recognized the potential benefits of incorporating lived experience into both

the research process and the development of interventions. Additionally, these individuals can play a crucial role in reducing stigma within healthcare settings.

Recommendations include using an algorithm to identify patients with an SMI in general practice. Primary care cooperatives can play a pivotal role in assisting their GPs by fostering interdisciplinary teamwork. The Dutch CVRM guideline was recently updated and now recommends using the QRISK3 calculator to evaluate the CVR for patients with an SMI. However, the guideline does not recommend assessing the CVR for all patients with an SMI. This is inconsistent with the Dutch multidisciplinary guideline for the care of people with SMI, which recommends annual screening. This thesis recommends that future guidelines should be consistent and developed in a more person-oriented and transdisciplinary approach, in collaboration with patients. Further research areas, beyond the TACTIC trial, should focus on identifying effective treatments for patients with both psychiatric and sleep disorders. Understanding patients' perspectives could help tailor approaches for inviting them to participate in studies. Additionally, interventions to reduce CVR that are suitable for young patients with an SMI should be explored.

Conclusion

In conclusion, the thesis emphasizes that while primary care in the Netherlands has taken on a larger share in managing SMI patients, significant gaps remain in addressing CVR. The TACTIC model presents a promising solution for integrating CVRM into primary care, enhancing collaboration, and tailoring care to the unique needs of SMI patients. If proven effective through the upcoming trial, TACTIC could serve as a scalable, evidence-based approach to improving health outcomes in this high-risk population. The thesis underlines the need for supportive health policies to sustain integrated care efforts, ultimately aiming to reduce the CVR-related mortality disparity experienced by SMI patients.

Samenvatting



Dit proefschrift onderzoekt de aard, omvang en uitdagingen van cardiovasculair risico management (CVRM) bij mensen met een ernstige psychische aandoening (EPA) vanuit het perspectief van huisartsen en ontwikkelt een interventie om hun cardiovasculair risico (CVR) te verminderen.

Hoofdstuk 1 biedt een algemene inleiding waarin de definitie van EPA is aangepast om beter aan te sluiten bij de eerstelijnszorg in Nederland. Deze nieuwe definitie omvat:

- Schizofrenie
- Bipolaire stoornis
- Psychose
- Chronisch gebruik van lithium of antipsychotica (AP), mits niet voorgeschreven voor dementie of delier.

Mensen met een EPA hebben een gemiddelde levensverwachting die 10-25 jaar korter is dan van de gehele populatie. Dit verschil wordt vooral veroorzaakt door het vroeger overlijden aan hart- en vaatziekten. Oorzaken van dit hoge CVR zijn onder meer bijwerkingen van antipsychotica, stress, ongezonde leefgewoonten en weinig toegang tot (preventieve) gezondheidszorg.

Sinds de Nederlandse overheid aanstuurde op een verschuiving van institutionele naar ambulante zorg in de psychiatrie is het aandeel van de zorg voor patiënten met een EPA in de eerste lijn toegenomen. Huisartsen spelen een cruciale rol bij het verbeteren van de algehele gezondheid, inclusief het CVR, van deze patiënten. Echter, ondanks dit beleid zijn de meeste huisartsen niet volledig toegerust om CVR bij EPA-patiënten te monitoren en behandelen. Dit proefschrift onderzoekt deze kloof en ontwikkelt een interventie om het CVR-management in de eerstelijnszorg te verbeteren.

Hoofdstuk 2 werd gepubliceerd als een redactioneel artikel met de titel “Het is tijd om in actie te komen”. Het doel was om zorgprofessionals bewust te maken van het verhoogde CVR bij patiënten met een EPA en hen aan te moedigen tot samenwerking.

Hoofdstuk 3 presenteert een observationele studie waaruit blijkt dat een hoog CVR bij patiënten met een EPA vaak over het hoofd wordt gezien in de eerstelijnszorg in Nederland. Slechts 8,5% van deze patiënten werd adequaat gescreend op CVR als ze geen diabetes mellitus (DM) of hart- en vaatziekte (HVZ) hadden. Een diagnose van DM of HVZ verhoogde de screeningspercentages respectievelijk tot 68,4% en 26,7%. Factoren zoals een hoge bezoekfrequentie, oudere leeftijd, het gebruik van antipsychotica en een COPD-diagnose

waren geassocieerd met een hogere screeningsgraad. De 1150 onderzochte patiënten die AP gebruikten, hadden in 32% van de gevallen een diagnose van schizofrenie, bipolaire stoornis of psychose, terwijl 68% dat niet had. Verder bleek dat AP-gebruikers zonder diagnose zich in verschillende opzichten onderscheidden van de groep met een diagnose, bijvoorbeeld door een hoger percentage vrouwen, meer gebruik van antidepressiva of CVR-verlagende medicatie, en een hogere bezoekfrequentie aan de huisarts.

Hoofdstuk 4 biedt inzichten uit interviews met huisartsen over hun perceptie van CVRM bij patiënten met een EPA. Huisartsen voelden zich verantwoordelijk voor de gezondheid van hun patiënten, maar waren zich vaak niet bewust van de verhoogde fysieke risico's en voelden zich niet zeker genoeg om AP-voorschriften te wijzigen. De samenwerking tussen psychiaters en huisartsen was beperkt, met weinig informatie-uitwisseling over CVRM. Ook twijfelden huisartsen eraan of patiënten wel voldoende zouden verschijnen op de jaarlijkse controles. Dit hoofdstuk pleit voor betere communicatiekanalen, expliciete richtlijnen voor risico-inschatting en voor management in de CVRM-richtlijn, en training voor huisartsen om hun vertrouwen in CVRM bij deze hoog risicogroep te vergroten.

Hoofdstukken 5, 6 en 7 beschrijven de ontwikkeling en het onderzoek naar het **T**ransmurale samenwerkingsmodel voor CVRM en medicatiebeoordeling bij patiënten met **A**ntipsy**C**ho**TIC**a (TACTIC). Deze interventie werd ontwikkeld in samenwerking met huisartsen, verpleegkundigen, psychiaters, medewerkers van GGZ-instellingen, ervaringsdeskundigen en gemeentelijke vertegenwoordigers in de regio Arnhem. Het doel was om de samenwerking in de zorg voor patiënten met een EPA te verbeteren op basis van de inzichten uit de voorgaande studies. De TACTIC-interventie, gefinancierd door ZonMw, werd getest en omvat drie stappen:

1. Voorlichting aan patiënten over een multidisciplinaire bijeenkomst om hen (en hun mantelzorgers) te motiveren en voor te bereiden.
2. Multidisciplinair overleg, waarin gepersonaliseerde behandeladviezen worden gegeven, inclusief richtlijnen voor het gebruik van atypische AP en strategieën voor het verminderen van andere CVR-factoren.
3. Gezamenlijk besluitvormingsconsult van de patiënt met de huisarts om een op maat gemaakt actieplan op te stellen op basis van de aanbevolen behandelingsopties.

Hoofdstuk 5 beschrijft een kwantitatief onderzoek naar de haalbaarheid van TACTIC. De resultaten toonden veelbelovende effecten. Drie maanden na de interventie hadden de deelnemers 41% van de adviezen opgevolgd, wat leidde tot een significante verbetering van

hun CVR. Vier op de tien rokers stopten succesvol met roken. Echter, het aantal deelnemers was lager dan verwacht en 36% voltooide de follow-up niet.

Hoofdstuk 6 beschrijft een kwalitatieve evaluatie van de haalbaarheid van de TACTIC-interventie, waarin zowel patiënten als zorgprofessionals werden bevraagd. Beide groepen concludeerden dat TACTIC met enkele aanpassingen haalbaar is. TACTIC is vooral nuttig voor patiënten met een hoog CVR, omdat het multidisciplinaire overleg dan effectiever is. Een belangrijk advies voor verbetering is optimaliseren van verwachtingsmanagement, bijvoorbeeld door een voorlichtingsgesprek met een ervaringsdeskundige of apotheker. Het uitnodigen van patiënten kost erg veel tijd, waar huisartsen niet over beschikken en daarom zullen zij ondersteuning nodig hebben om voldoende patiënten te kunnen benaderen.

Hoofdstuk 7 beschrijft het onderzoeksprotocol voor de (kosten)effectiviteitsstudie van TACTIC. Na zorgvuldige overweging werd gekozen voor een incomplete stepped wedge cluster randomized design, waarbij de primaire uitkomsten het cardiovasculaire risico (gemeten met de QRISK3-score) en de mentale gezondheid (MHI-5) zijn.

Hoofdstuk 8, de algemene discussie, vat de belangrijkste bevindingen samen en vergelijkt deze met recente literatuur. De prevalentie van EPA in de eerstelijnszorg is ongeveer 1,5% van de volwassen bevolking. In Nederland wordt CVR-screening bij deze groep onvoldoende uitgevoerd, in tegenstelling tot in het Verenigd Koninkrijk, waar 68% van de patiënten met een EPA jaarlijks wordt gescreend. Bovendien schrijven huisartsen AP vaak off-label voor, vooral bij slaapproblemen met psychiatrische comorbiditeit. Interventies van andere onderzoekers om CVRM te verbeteren in de eerste lijn kampen met vergelijkbare uitdagingen op het gebied van patiëntdeelname en therapietrouw, wat de noodzaak van multidisciplinaire samenwerking onderstreept. Ervaringsdeskundigen spelen een waardevolle rol bij het verbeteren van patiëntbetrokkenheid en het verminderen van stigma in de zorg.

Aanbevelingen in dit hoofdstuk omvatten het gebruik van een algoritme voor de huisarts om patiënten met een EPA te identificeren in de eigen praktijk en het bevorderen van multidisciplinaire samenwerking vanuit zorggroepen. De recent geüpdatete Nederlandse CVRM-richtlijn beveelt nu QRISK3 aan voor het schatten van het CVR van patiënten met een EPA, maar systematische jaarlijkse CVR-screening wordt niet aanbevolen, wat in tegenspraak is met de multidisciplinaire Zorgstandaard EPA. Dit proefschrift pleit voor consistentere multidisciplinaire richtlijnen, die mede ontwikkeld worden met ervaringsdeskundigen, zodat

het patiënten perspectief voldoende belicht wordt. Verder onderzoek, naast de TACTIC-trial, moet zich richten op behandelingen voor patiënten met zowel psychiatrische als slaapstoornissen en op CVR-reductie bij jongere EPA-patiënten.

Conclusie

Hoewel de eerstelijnszorg in Nederland een grotere rol heeft gekregen in de zorg voor patiënten met een EPA, blijven er aanzienlijke hiaten bestaan in het CVRM voor deze groep. Het TACTIC-model biedt een veelbelovende oplossing voor de integratie van CVRM in de eerstelijnszorg, het verbeteren van samenwerking en gepersonaliseerde zorg voor patiënten met een EPA. Als deze interventie effectief blijkt in de aanstaande trial, kan TACTIC een schaalbare, evidence-based aanpak worden om de gezondheidsuitkomsten van deze hoog risicogroep te verbeteren. Dit proefschrift benadrukt de noodzaak van ondersteunend gezondheidsbeleid om geïntegreerde zorg te verduurzamen en zo de CVR-gerelateerde sterfte onder patiënten met een EPA te verminderen.

Chapter 10

Research Data Management



Ethics and privacy

This thesis is based on the results of research involving human participants, which were conducted following relevant national and international legislation and regulations, guidelines, codes of conduct, and Radboudumc policy.

Our study protocols have all been reviewed by the Medical Ethics Review Committee 'METC Oost-Nederland'. A statement that the study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO), was obtained from the METC Oost-Nederland. The file numbers of the studies in Chapters 3, 4, and 5&6 are 2019-5515, 2019-5186, 2020-7240, and 2022-15835.

The participants' privacy in these studies was ensured through pseudonymization. The pseudonymization key was stored on a secure network drive accessible only to project members who required access due to their roles. The pseudonymization key was stored separately from the research data.

Informed consent was obtained from participants to collect and process their data for all research projects (Chapters 3-6). For Chapter 5 consent was also obtained for sharing the (pseudonymized) data after research. For Chapter 4 and 6 the sensitivity and confidentiality of the raw qualitative data (i.e. interviews, forum groups) makes sharing of the data without compromising confidentiality and privacy impossible, therefore consent for sharing of the raw data was not asked from the participants.

Data collection

Patient-level data on CVRM for patients with SMI and/or AP was obtained from the Radboudumc Technology Centre (RTC) Health Database for the study in Chapter 3 and stored in *DRE Portal (mydre.org)* during the research process. The interviews from Chapters 4 and 6 were recorded, pseudonymized, and stored in Atlas-Ti on the department server, which is accessible only by our project members. For the patient-level data from the TACTIC pilot (Chapter 5), we obtained pseudonymized data from the electronic medical records (EMRs) of the participating general practices using VIPlive, and we collected questionnaires through Castor EDC.

Data storage

The data will be saved for 15 years after termination of the study. The data from Chapter 6 are stored on the department server, only accessible by our project members working at the Radboudumc, until K.J. van den Brule-Barnhoorn will archive them. The access codes to de-pseudonymize the participants of the study in Chapter 5 and 6 are stored on a separate server in a locked file that is only accessible to a limited number of project members. Paper forms are kept in a secure archive at the Department of Primary and Community Care at Radboud University Medical Center. This includes informed consent forms and questionnaires filled out by participants who were unable to respond digitally.

Data sharing according to the FAIR principles

The data from Chapters 3, 4, and 6 is not suitable for reuse and will be archived for 15 years in DACs of the Radboud Data Repository after termination of the study (see table below for the DOIs). The processed data and documentation from the feasibility study (Chapter 5) were published with restricted access in the Data Sharing Collection within the Radboud Data Repository (DOI: https://doi.org/10.34973/19s3-d625). Requests for access will be checked by Dr. M. Perry, L.

Peters-van Gemert, and K.J. van den Brule-Barnhoorn, e.g. the PI, data steward of the department, and data manager, against the conditions for sharing the data as described in the signed Informed Consent. This dataset includes the published article, SPSS files, codebook and a readme file. The metadata is visible and indexed by search engines, maintaining a balance of being “as open as possible, as restricted as needed.” All studies are published with open access.

**The table below details where the data and research documentation for each chapter can be found on the Radboud Data Repository (RDR). All data archived as a Data Sharing Collection remain available for at least 15 years after termination of the studies.*

Chapter	*DAC*	***DSC***	***DSC License***
3	*DOI: 10.34973/jjnw-dy89*		
4	*DOI: 10.34973/7zsf-4b25*		
5		*DOI: 10.34973/19s3-d625*	*RUMC-RA-DUA-1.0*
6	*Will be archived by K.J. van den Brule-Barnhoorn after publication of an article*		

DAC = Data Acquisition Collection, DSC = Data Sharing Collection

Dankwoord

Er zijn veel mensen en organisaties die mij vooruit hebben geholpen door het delen van hun kennis, inspanningen en inspirerende gedachten. In dit hoofdstuk wil ik iedereen die een bijdrage leverde hartelijk danken voor hun hulp: de medewerkers van de afdeling Eerstelijnsgeneeskunde van het Radboudumc; de TACTICplus-werkgroep; Onze Huisartsen; de werkgroep EPA; de huisartsenpraktijken die deelnamen aan het TACTIC onderzoek; Pro Persona, GGNet en andere GGZ-instellingen; de apothekers van de CAA; de ervaringsdeskundigen van Ixta Noa (voorheen Vitale Verbindingen) en RIBW.

Alle patiënten die deelnamen aan TACTIC ben ik heel dankbaar. In het groepsgesprek kwamen zeer persoonlijke zaken op tafel te liggen. Sommigen van jullie hebben zich ook laten interviewen en maakten duidelijk dat we veel van jullie vroegen.

Sommige mensen wil ik graag persoonlijk bedanken:

Marion, jij begeleidde mij vanaf het eerste moment en bleef tot het klaar was. Ik had veel steun aan jouw scherpe blik. Voor elk probleem had je altijd minstens drie mogelijke oplossingen.

Erik, jij kan als geen ander de rode draad vasthouden. Dat kwam goed van pas bij dit ingewikkelde project. Je was voor mij een grote steun met jouw optimistische kijk op de zaak.

Jan, veel dank voor al jouw kennis over zowel kwalitatief én kwantitatief onderzoek doen. Jij wist overal een leerzame aanvulling bij te geven. Jouw humor tijdens onze overleggen vond ik sfeer verhogend.

Karlijn, soms was je me voor met jouw scherpe brein. Dank voor je geduld. Ik hoop en verwacht dat je de kennis over CVRM voor mensen met een EPA verder kunt vergroten.

Peter, dank voor je grote bijdrage aan alle kwalitatieve onderdelen van de onderzoeken in dit proefschrift en voor je deelname aan de adviesgroep. Ik kon altijd rekenen op goede en snelle feedback van jou, waarmee ik weer verder kon.

Wim, Reinier en Bianca, dank voor jullie geduld met mij als buitenpromovenda, met enige achterstand op de jongere generatie in de statistiek en met SPSS, en voor jullie hulp waar nodig.

Wiepke en Joost, jullie waren onmisbaar als psychiaters met een goed inzicht in de huisartsgeneeskunde. Jullie waren van grote waarde in het hele traject. Wiepke, dat jij zelfs inviel bij een MDO tijdens de trial vond ik echt geweldig.

Maria, dank dat je bereid was om mijn promotor te zijn. Het werd je misschien een beetje in de maag gesplitst, maar je bleef altijd heel positief en ik heb dat als zeer steunend ervaren.

Iris, je was mijn mentor en gaf me mee dat als het onderwerp makkelijk was, je er geen promotietraject aan hoefde te besteden. Dank voor de pep talks.

Twanny, je wist altijd antwoord op mijn vragen over de meest uiteenlopende zaken (betalingen en vergoedingen, een artikel gepubliceerd krijgen, functies van Atlas-ti, bij wie ik moest zijn). Als ik het echt niet meer wist, dacht ik: “Misschien weet Twanny het”, en ja hoor… Je hielp me bovendien nog met het maken van dit boekje. Heel veel dank daarvoor!

Jet en Noor, de samenwerking met jullie kenmerkte zich door het elkaar moeiteloos aanvoelen en aanvullen bij alle inspanningen om CVRM voor patiënten met een EPA in onze regio te borgen. Ik heb daarvan genoten.

Dominique, dank voor het maken van al die filmpjes voor TACTIC en voor de rust die je uitstraalde als ik zenuwachtig werd.

Eric, Mario en Martine van SHO (nu Unilabs), dank voor jullie bereidheid mee te denken in de zoektocht naar een werkwijze om labaanvragen te doen voor TACTIC. We hebben daar veel aan gehad en het was een erg prettige samenwerking.

Mireille, jij was degene die mij via de HartvaatHAG erop attendeerde dat mensen met een ernstige psychische aandoening (EPA) een verhoogd vaatrisico hebben.

René, Raymond, Mireille en Jolanda, ik voelde me enorm gesteund toen jullie onze pilotpraktijk wilden zijn.

Elvira en Niels, jullie hielpen me in de eindfase enorm met jullie aanmoedigingen en advies voor de laatste loodjes. Niels, dank voor je frisse blik waarmee ik de onduidelijkheden uit dit proefschrift kon wegwerken.

Rudy, dank dat je je door mij liet interviewen voor het onderzoek van hoofdstuk 4 en dat jij en Marijke vervolgens ook pilotpraktijk wilden zijn voor TACTIC.

Dorien en Merlijn, wat hebben jullie veel patiënten in deze doelgroep! Ik bewonder jullie moed om als pilotpraktijk mee te doen. Door al die patiënten en het feit dat wij alles nog moesten leren en uitproberen, was het een enorme klus voor jullie. Ik ben heel dankbaar dat jullie het hebben doorgezet.

Toon, wat heerlijk dat je ons hielp met de MDO's. Bij PLEKvoorEPA kon ik zelf ervaren hoe je dat deed. Ik noemde dat 'op-het-puntje-van-je-stoel-MDO's'. Tijdens de uitvoering van de TACTIC-pilot konden andere huisartsen dat ook ervaren. Samen om tafel zitten leidt tot meer begrip voor elkaars werkwijze. Het was een groot plezier om met je te mogen werken.

Janite en Jeroen, dank voor jullie hulp bij de voorbereidingen en uitvoering van de TACTIC-pilot. Ik heb van jullie geleerd wat ervaringsdeskundigen kunnen betekenen voor anderen. Het was nieuw voor mij en ik vond het fascinerend. Inge, jij zat in onze adviesgroep en hielp ons met de trial. Ook de andere ervaringsdeskundigen die in de werkgroep EPA of aan de trial deelnamen, steunden ons met raad en daad. De invalshoek van ervaringsdeskundigheid kan niet overschat worden bij een interventie als TACTIC.

Frank, Kim en Yasmin, dank voor jullie advies vanuit de invalshoek van apothekers. Jullie bijdrage aan de vorming van de interventie TACTIC en jullie deelname aan de pilot waren erg waardevol.

Marieke, mijn lieve moeder, bedankt voor je steun en je toenemende enthousiasme naarmate de afronding naderde. De moestuin zal er straks vast mooier bijliggen nu het onderzoek klaar is. Jammer dat Jef, mijn vader, dit niet mee kon maken. Ik had er graag met hem over willen praten. Hij had de statistische details van de trial met het bijzondere design vast heel interessant gevonden.

Tenslotte mijn gezin, waarmee ik mij zeer gezegend voel: Sabine en Femke, mijn dochters en paranymfen. Wat is dat mooi! Jullie hielpen me nu en dan met de Engelse taal en SPSS, en door blijk te geven van groot vertrouwen in mijn kunnen. Heel veel dank voor jullie niet-aflatende support.

Pieter, mijn lief, wat was het heerlijk dat jij naast me stond tijdens alle pieken en dalen. De illustraties die je maakte voor onze patiëntenfolder en die ook in dit proefschrift zijn opgenomen, zijn prachtig. Jouw liefde, zorgzaamheid en humor hielpen me om de eindstreep te halen.

Department: **Eerstelijnsgeneeskunde**
PhD period: **31/07/2017 – 28/02/2025**
PhD Supervisor(s): **Prof. M van den Muijsenbergh**
PhD Co-supervisor(s): **Dr. M.C.J. Biermans, Dr. J. van Lieshout, Dr. E.W.M.A. Bischoff**

Training activities	Hours
Courses	
- Radboudumc - eBROK course (2017)	42,00
- RIHS PhD introduction course (2018)	15,00
- Introductiecursus kwalitatief onderzoek in de gezondheidszorg (2019)	28,00
- Radboudumc - Scientific integrity (2021)	20,00
- DGS - Scientific Integrity Course (2021)	7,00
- RU - Statistiek voor promovendi met SPSS (2021)	56,00
- RU - Writing Scientific Articles (2022)	84,00
- Radboudumc - Re-registration BROK (2022)	26,00
- CARE dagen (2024)	28,00
- Huisarts en Wetenschap bijeenkomst (2024)	2,00
- Social media workshop (2024)	2,00
Seminars	
- EBM refereerbijeenkomst Vascular damage ELG oral (2017)	4,00
- EBM refereerbijeenkomst ELG: Antipsychotica in de eerste lijn, onze zorg? Oral 2020	4,00 4,00
- Trimbos instituut “Bijeenkomst somatische screening bij EPA” oral (2023)	4,00
- Werkconferentie ‘Herstel voor iedereen’ oral (2020)	4,00
- Werkconferentie UMC Utrecht “Integrale zorg voor mensen met lichamelijke en psychische aandoeningen” oral (2023)	
Conferences	
- WONCA (Presented abstract: Cardiovascular risk management in patients with severe mental illness or taking antipsychotics: a qualitative study on barriers and facilitators among Dutch general practitioners) 2021 oral	36,00
- NHG wetenschapsdag (presentatie abstract: Transmural collaborative care model for the review of antipsychotics: a feasibility study of a complex intervention) 2022 oral	14,00
Teaching activities	
Lecturing	
- Hartcursus aan huisartsen opleiding Radboud 2018, 2019, 2020	4,00
- EPA scholing voor Zorggroep Onze Huisartsen Arnhem e.o. (2021)	4,00
- Farmacotherapeutisch overleg over antipsychotica in Arnhem (huisartsen en apothekers) 2021	4,00
- EPA scholing voor Huisartsen Zorggroep Oude IJssel (huisartsen en praktijkondersteuners) 2023	4,00
- EPA scholing voor Zorggroep Onze Huisartsen Arnhem e.o. (huisartsen en praktijkondersteuners) 2023	4,00
	4,00

- CVRM voor ernstige psychische aandoeningen (EPA) VOHA keuzeonderwijs 2023, 2024	4,00
- CVRM voor EPA VOHA voor opleiders 2023	4,00
- EPA scholing voor Huisartsen Zorggroep Oude IJssel (2023)	4,00
- CVRM scholing voor Verpleegkundig specialisten Pro Persona (2024)	
Supervision of internships	
- Supervision Master student internship Anne Posthuma 2017	28,00
- Supervision Bachelor students internship of HAN Medisch Hulpverlener, Nina Drijfholt & Monique Vaneker 2018	28,00
- Supervision Master student internship Latoya Lautan 2019	28,00
- Supervision Master student internship Tim Massa 2020	28,00
- Supervision Master student internship Hanne Vrusch 2023	28,00
Other activities	
Networking	
- Werkgroep EPA regio Arnhem t.b.v. Onze Huisartsen (2017-heden)	20,00
- Voorzitter Carel Bakx Hartvaathag prijs (2018-heden)	4,00
- Benaderen van huisartsen, psychiaters, ervaringsdeskundigen en apothekers t.b.v. de TACTIC trial in Arnhem, Nijmegen, Deventer, Rotterdam, Amsterdam en Utrecht (2022)	60,00
- Hoofdonderzoeker TACTIC trial coördinatie en uitvoering van eerste wave (2023)	60,00
- Klankbordgroep starterskit somatische screening Phrenos (2024)	1,00
Total	**701**

Curriculum Vitae of K.M. Jakobs

Kirsti Jakobs
Born: 10 March 1969, Wageningen, Netherlands
Daughter of Jef Jakobs and Marieke Coops

Kirsti Jakobs graduated from Erasmus College in Zoetermeer in 1988. She obtained her medical degree from Erasmus University Rotterdam in 1996. During her studies, she developed a keen interest in research, participating in various projects, including an investigation into *Plasmodium falciparum* resistance to chloroquine in Côte d'Ivoire, West Africa (University of Agriculture, Wageningen), as well as studies on the inverse relationship between NSAID use and Alzheimer's disease, and the impact of life events in general practice (Erasmus University Rotterdam).

After graduating in 1996, Kirsti worked as a junior resident in the Departments of Cardiology and Internal Medicine at Het Holy Ziekenhuis in Vlaardingen. In 2001, she completed her training as a general practitioner in Rotterdam.

From 2002 to 2004, Kirsti worked as a GP in the practice of Dr. Jan van Lieshout, after which they established a medical partnership that lasted until 2010. She continued working as a part-time general practitioner in various practices, which allowed her to develop a special interest in cardiovascular diseases. For the past eight years, she has been employed at Huisartsenpraktijk de Mussenberg in Elst.

In 2011, Kirsti co-initiated the Cardiovascular Risk Management (CVRM) program for the Primary Care Cooperative in the Arnhem region, together with Dr. Carel Bakx. In 2014, she completed the NHG expert training program for general practitioners specializing in cardiovascular diseases at Maastricht University. During this training, she became increasingly aware of the elevated cardiovascular risk among patients with severe mental illnesses—a group notably underrepresented in cardiovascular prevention programs.

In 2017, Kirsti raised this issue with the Department of Primary and Community Care. The Primary Care Cooperative, where she has been working since 2011, generously supported her PhD trajectory by providing financial assistance for her research. After several years of securing additional funding, she officially embarked on her PhD journey, which led to the launch of a clinical trial addressing this crucial issue.

Kirsti is married to Pieter van der Drift, and they have two daughters, Sabine and Femke.



Radboudumc
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Radboud University